酸棗仁

酸棗仁藥用之名，始載於神農本草經，列為上品

1. 神農本草經：味酸，平。主治心腹寒熱，邪結氣，四肢酸疼濕痺。久服安五臟。
2. 名醫別錄：無毒。主治煩心不得眠，臍上下痛，血轉久泄，虛汗，煩渴，補中，益肝氣，堅筋骨，助陰氣，令人肥健。

酸棗仁

3. 藥性論：主筋骨風。炒末作湯服之。
4. 日華子本草：治臍下滿痛。
5. 開寶本草：煩心不得眠，臍上下痛，血轉久泄，虛汗，煩渴。補中益肝氣，堅筋大骨，助陰氣，令人肥健。

酸棗仁

6. 太平聖惠方：膽虛不眠，寒也。酸棗仁炒香，竹葉湯調服。
7. 皇祐簡要濟眾方：膽實多睡，熱也。酸棗仁生用，末茶、薑汁調服。

酸棗仁

8. 本草綱目：棗仁，味酸性收，故主肝病，寒熱結氣，酸痺久泄，臍下滿痛之症。其仁甘而潤，故熟用療膽虛不得眠、煩渴虛汗證；生用療膽熱好眠，皆足厥陰、少陽藥也。今人專以為心家藥，殊昧此理。

註：

足厥陰-肝經

足少陽-膽經

酸棗仁

9. 明。繆希雍-本草經疏：

- 酸棗仁得木之氣而兼土化，故其實酸平，仁則兼甘，氣味勻齊，其性無毒，為陽中之陰。入足少陽，手少陰，足厥陰，太陰之經。
- 專補肝膽，亦復醒脾，從其淡也。熟則芳香，香氣入脾，故能歸脾。能補膽氣，故可溫膽。

酸棗仁

9. 明。繆希雍-本草經疏：

- 母子之氣相通，故亦主虛煩，煩心不得眠。
- 其主心腹寒熱，邪結氣聚，及四肢酸疼濕痺者，皆脾虛受邪之病，脾主四肢故也，膽為諸臟之首，十一臟皆取決於膽，五臟之精氣皆稟於脾。故久服之，功能安五臟，輕身延年也。

酸棗仁

10. 小結：

棗仁生用味甘，性平，功效清肝膽虛熱、寧心安神；炒後增強醒脾補陰、斂汗寧心之功。臨床用名有酸棗仁、炒酸棗仁。

酸棗仁

- 【來源】為鼠李科植物酸棗Ziziphus jujuba的乾燥成熟種子。
- 【性味與歸經】甘(酸)，平。歸心、肝經。
- 【功效】養心安神，斂汗。鎮靜安神、降壓藥。為治療虛煩不眠的常用藥。用於：
  - 驚悸失眠適用於血虛而致的心煩、不眠。
  - 體弱多汗、虛汗盜汗。

酸棗仁治肝膽不足，虛煩不得眠
黃連治心火亢盛，心中煩熱不得眠

酸棗仁(右炒)(扁圓形或橢圓形,赤褐,光滑光澤裂紋,
種皮脆胚乳白,子葉淡黃)

【應用 I】

- 用於失眠、驚悸
  - 本品能養心陰，益肝血而寧心安神， 滋養性安神藥，主要用於心肝血虛引起的失眠、驚悸怔忡等證。可配當歸、白芍、何首烏、龍眼肉等同用
    - 若肝虛有熱之虛煩失眠，常與知母、茯苓等合用，如酸棗仁湯
    - 若心腎不足、陰虛陽亢所致虛煩失眠、心悸、健忘、口燥咽乾、舌紅少苔者，可配生地黃、玄參、柏子仁等養心滋腎藥同用，如天王補心丹。

- 酸棗仁湯
  - 酸棗仁、茯苓、知母、川芎、甘草
  - 肝血不足，陰虛內熱，心神失養證(虛勞)
- 天王補心丹
  - 生地、天冬、麥冬、酸棗仁、柏子仁、當歸、人參、茯苓、遠志、五味子、玄參、丹參、朱砂、桔梗
  - 心腎兩虛，陰虛血少，虛火內擾證(虛弱體質精氣神血不足或損傷所引起之失眠、心神不寧...症狀)
- 甘麥大棗湯
  - 小麥、甘草、大棗
  - 肝鬱心虛臟躁證；神經衰弱，精神官能症

【應用 II】

- 用於體虛自汗、盜汗等證。有斂汗作用
  - 常配黨參、五味子、山茱萸等同用。

【本草備要】

- 性味：甘酸而潤。
- 功能：
  - 專補肝膽，炒熟酸溫而香，亦能醒脾。
  - 助陰氣，堅筋骨，除煩止渴，斂汗，甯心。
- 主治：
  - 療膽虛不眠，酸痺久瀉。
  - 生用酸平，療膽熱好眠。

酸棗仁生用甘酸而潤，偏用於肝膽虛熱之證。
炒熟用則酸溫而香，兼有醒脾作用，偏用於肝、膽、心、脾血虛少眠之證。

酸棗仁

- 鼠李科(Rhamnaceae)植物酸棗*Ziziphus jujuba* Mill.var.spinosa (Bge.) ）Hu ex H. F. Chou,其乾燥酸棗的種子.中藥名:酸棗仁.
- 屬名:棗屬Ziziphus :希zizyphon棗原名.
  來自阿拉伯 zizouf 酸棗
- 種名:jujuba 英 jujube 棗實.
- 種名:spinosa:針刺的.多刺的.有刺的.
- 註:ex: according to , from
  et: and

枝節上有直的和彎曲的刺

酸棗仁

酸棗仁化學成分

- 酸棗仁種子含:

  1.三萜及三萜皂苷類成分:

  酸棗仁皂苷A、B、D、E(jujubosides A-B、D-E)

  白樺脂酸(betulic acid)

  白樺脂醇(betulin)

  美洲茶酸(cenothic acid)

  2.黃酮類成分:

  spinosin、isospinosin、當歸素(swertisin)、葛根素(puerarin)

  3.生物鹼類成分:

  酸棗仁鹼A、E、K、Ia、Ib

  (sanjoinine A、E、K、Ia、Ib) , juzirime

酸棗仁藥理作用

1.鎮靜催眠

(生酸棗仁和炒酸棗仁中的皂苷類和黃酮類成分均有顯著的鎮靜催眠作用.)

2.增強學習記憶

3.抗氧化

(酸棗仁總黃酮能顯著清除$O_2\cdot$, $\cdot OH$,$H_2O_2\cdot$三種自由基)

4.耐缺氧

(酸棗仁總皂苷能保護大鼠心肌細胞)

5.抗腫瘤

6.抗焦慮,降血脂,降血糖

酸棗仁湯對於焦慮症、癲癇症之治療效果

評估及作用機轉之研究

謝明村 [redacted]

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緒　　言

酸棗仁湯收載於漢、張仲景著金匱要略，主治虛勞虛煩不得眠，歷代中醫臨床均沿用於治療失眠症。著者等以現代藥理實驗證實本方劑對於動物具有鎮靜及抗痙攣作用；且在臨床評估對失眠症、焦慮症亦具有療效。本實驗進行酸棗仁湯對於大白鼠自發運動量與中樞腦內單胺濃度之影響，俾瞭解其藥理的作用機轉。

酸棗仁湯的藥物基原

酸棗仁	Zizyphus *spinosus* Hu (Rhamnaceae),
茯 苓	Poria *cocos* (Schw.) Wolf (Polyporaceae),
芎 藭	Ligusticum *chuanxiong* Hort (Umbelliferae),
知 母	Anemarrhena *asphodeloides* Bunge (Liliaceae),
甘 草	Glycyrrhiza *uralensis* Fischer et Dc. (Leguminosae).

酸棗仁湯

組　　成：酸棗仁二至四錢，知母三錢，川芎一至錢半，甘草二錢，
茯苓三錢。

功用主治：除虛煩，寧心神。治心煩不眠、眠則多夢、易驚
醒、頭脹痛、煩燥易怒。

一、酸棗仁 (Zizyphi Spinosi Semen)：

性味歸經：性平，味甘、酸。入肝、膽、心、脾經。

藥　　能：甘酸而潤，專補肝膽，除煩解渴、斂汗。療膽虛不眠。

修　　治：生用或炒用。

成　　分：含三萜類化合物，主為Betulic acid。

　　　　　另含皂苷，主為jujuboside A及B。

藥　　理：(1) 鎮靜催眠作用。

　　　　　(2) 鎮痛、抗驚厥、降溫作用。

　　　　　(3) 降壓及抗心率不整作用。

三、川芎 (Ligustici Rhizoma)：

性味歸經：性溫，味辛。入肝、膽、心包經。

藥　　能：活血行氣，祛風止痛。

成　　分：含生物鹼、揮發油、阿魏酸等。

藥　　理：(1) 擴張冠狀動脈。

(2) 擴張周邊血管及降低血壓。

(3) 抑制血小板聚集及抗血栓形成。

(4) 鎮靜作用。

二、知母 (Anemarrhenae Rhizoma)：

性味歸經：性寒，味苦。入肺、胃、腎經。

藥　　能：上清肺金而瀉火，下潤腎燥而滋陰。
治傷寒煩熱，燥渴虛煩。

成　　分：根莖含皂苷Timosaponins、Sarsasapogenin、Markogenin。

藥　　理：(1) 清熱養陰。
(2) 止血瀉火。
(3) 利尿消腫。

五、茯苓 (Poria)：

性味歸經：性溫，味甘。入肺經。

藥　　能：利尿滲濕、健脾補氣、寧心益氣，安魂定魄。

成　　分：含Pachyman、Ergosterol，有效成分未詳。

藥　　理：(1) 利尿作用。

(2) 增強免疫作用。

(3) 鎮靜作用。

四、甘草 (Glycyrrhizae Radix)

性味歸經：味甘，生用氣平，炙用氣溫。通行十二經。

藥　　能：(1) 生用補脾胃不足，而瀉心火。

(2) 炙用補三焦元氣，而散表寒。

(3) 解百藥毒。

成　　分：主含三萜類化合物甘草甜素Glycyrrhizin和甘草次酸Glycyrrhizic acid。

藥　　理：(1) 腎上腺皮質激素樣作用。

(2) 抗炎及抗變態反應作用。

(3) 解毒作用。

(4) 鎮咳作用。

實驗材料之製備

本實驗所使用之酸棗仁湯，係依金匱要略所載的藥材及劑量配方。五種藥材爲酸棗仁、茯苓、芎藭、知母、甘草（均購自台中全壽堂中藥商）。以95％乙醇作溶媒，抽取液經減壓濃縮、冷凍乾燥製得粗抽取物。使用時以0.5％CMC溶液配製爲懸浮液。

Acute Toxicity of Suanzaorentang Ext. in Mice

DRUG	ROUTE	LD50(gm/kg)	(95% Confidence limit)
S.T.	P.O.	>10	
	I.P.	3.2	(2.5-4.1)
S.T.-H_2O	P.O.	>10	
	I.P.	2.5	(2.1-2.9)

S.T.: 95% ethanol ext. of Suanzaorentang

S.T.-H_2O: water ext. of Suanzaorentang

Effects of Sauzaorentang ext. on the Pentylenetetrazol-induced Convulsion in mice

DRUG	DOSE(g/kg)	No.of animal	C.C.(min.)	T.C.(min.)	Incidence of Pot.	D/N
Control		10	0.61±0.03	3.04±0.28	0	10/10
S.T.	1.5	10	0.64±0.03	4.06±0.42	1	10/10
	3.0	10	0.66±0.03	5.04±0.37***	2	10/10
	6.0	10	0.66±0.03	6.19±0.52***	5	10/10
S.T.-H_2O	6.0	10	0.60±0.03	4.14±0.35*	1	10/10
Ziziphus	6.0	10	0.64±0.03	4.66±0.54*	2	10/10
Poria	6.0	10	0.61±0.03	3.12±0.40	0	10/10
Ligust.	6.0	10	0.71±0.03	6.22±0.46***	6	10/10
Anemarr.	6.0	10	0.60±0.02	3.08±0.43	0	10/10
Gly.	6.0	10	0.58±0.03	3.37±0.39	0	10/10

C.C.: onset of clonic convulsion.
T.C.: time of c.c. to tonic convulsion.
Incidence of Potentiation: 2 times of control.
D/N: No. of death/No. of animal tested.

* $p<0.05$ *** $p<0.001$

Effects of Suanzaorentang ext. on the Picrotoxin-induced convulsion in mice

DRUG	DOSE(g/kg)	No. of animal	C.C.(min.)	T.C.(min.)	Incidence of pot.	D/N
Control		10	6.23±0.17	5.67±0.43	0	10/10
S.T.	1.5	10	6.22±0.25	5.41±0.45	0	10/10
	3.0	10	7.12±0.20**	6.31±0.26	0	10/10
	6.0	10	7.81±0.40**	8.85±0.42***	0	10/10
S.T.-H_2O	6.0	10	6.43±0.21	5.75±0.59	0	10/10
Ziziphus	6.0	10	6.18±0.34	6.00±0.44	0	10/10
Poria	6.0	10	6.35±0.36	5.74±0.40	0	10/10
Ligust.	6.0	10	6.97±0.30*	6.93±0.44	0	10/10
Anemarr.	6.0	10	6.55±0.11	6.21±0.35	0	10/10
Gly.	6.0	10	6.42±0.21	6.17±0.36	0	10/10

C.C.: onset of clonic convulsion.
T.C.: time of C.C. to tonic convulsion.
Incidence of potentiation: 2 times of control.
D/N: No. of death/No. of animal tested.

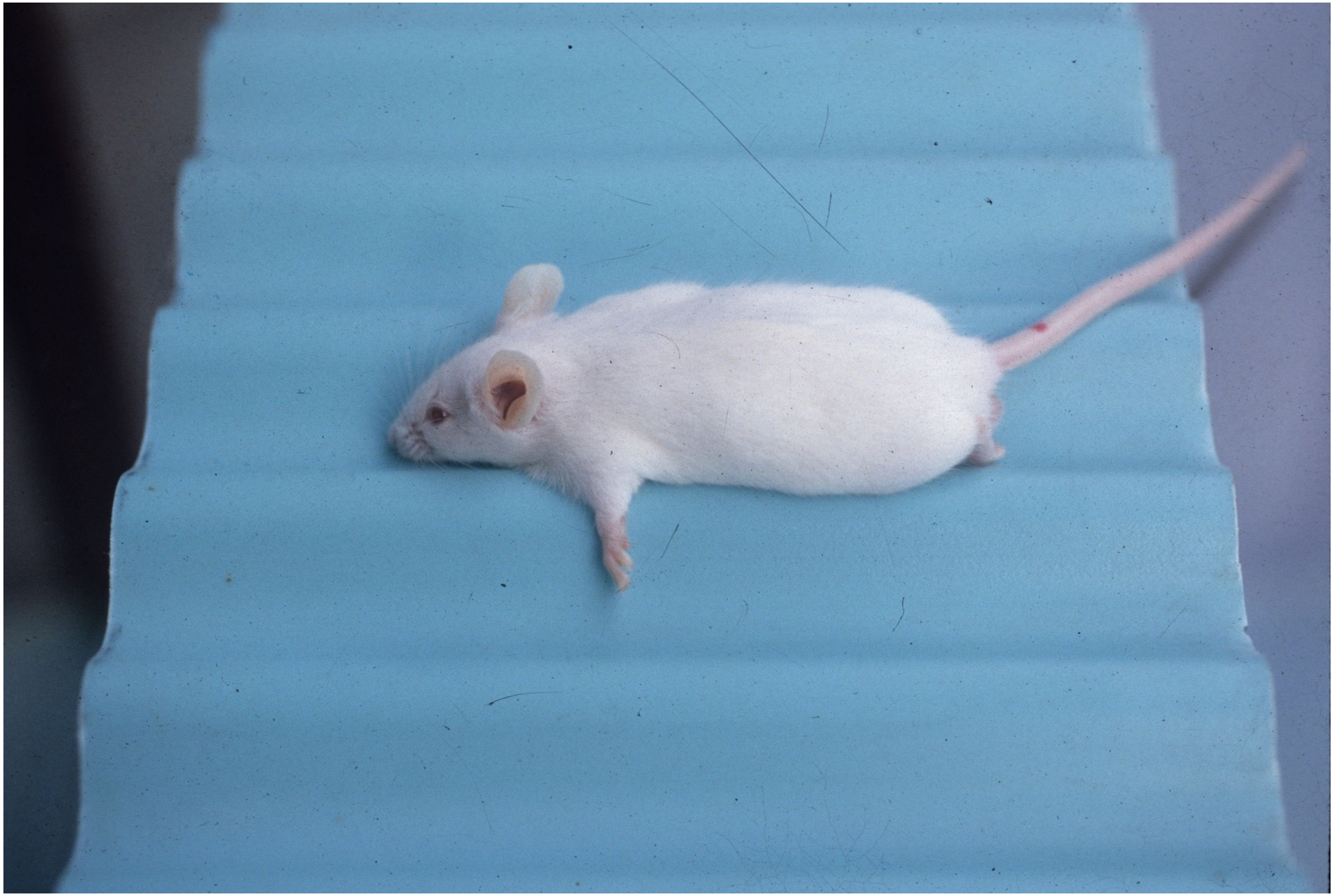
* $p<0.05$ ** $p<0.01$ *** $p<0.001$

Effects of Sauzaorentang ext. on the Hexobarbital-induced hypnosis in mice

DRUG	DOSE(g/kg)	No. of animal	Onset(min.)	Sleeping time (min.)	Incidence of Potentiation
Control		10	8.41±0.50	37.70±2.79	0
S.T.	1.5	10	7.72±0.46	51.00±2.91**	0
	3.0	10	6.96±0.25*	74.80±4.40***	4
	6.0	10	6.57±0.22**	85.10±6.96***	6
S.T.-H_2O	6.0	10	8.79±0.58	39.00±2.25	0
Ziziphus	6.0	10	7.40±0.44	61.30±2.96***	1
Poria	6.0	10	8.60±0.46	36.88±3.45	0
Ligust.	6.0	10	7.68±0.57	45.00±2.09	0
Anemar.	6.0	10	8.74±0.50	36.70±4.55	0
Gly.	6.0	10	7.86±0.45	44.55±5.36	0

Onset: righting reflex disappear.
Sleeping time: time of onset to righting reflex recover.
Incidence of Potentiation: two times of control.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$



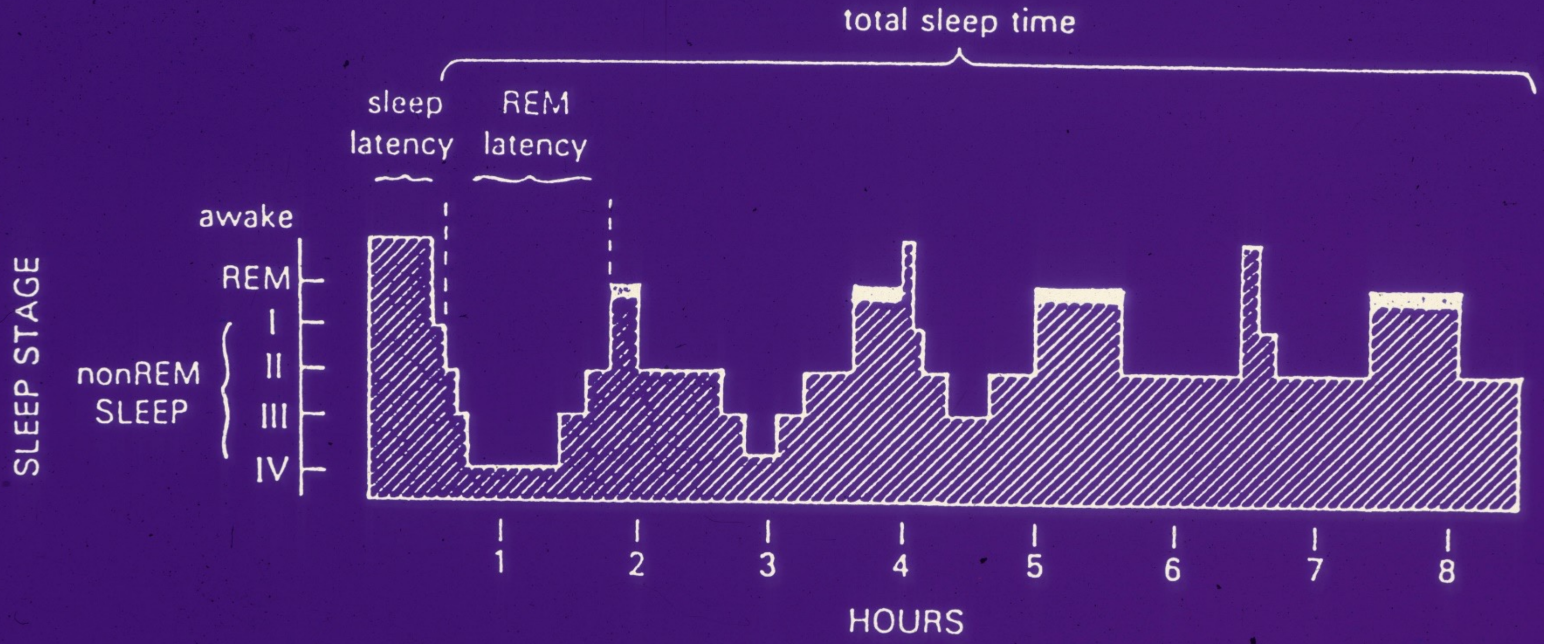
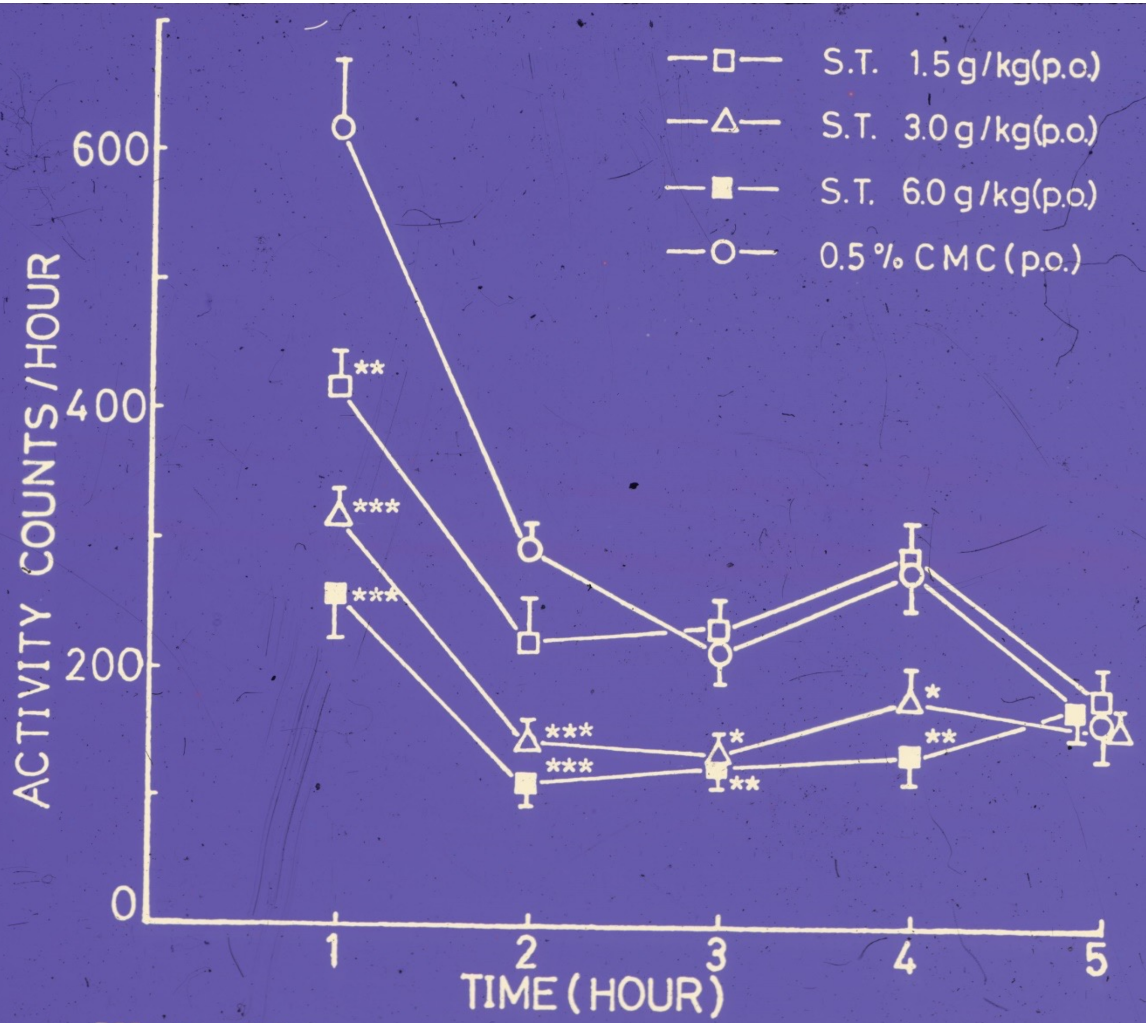
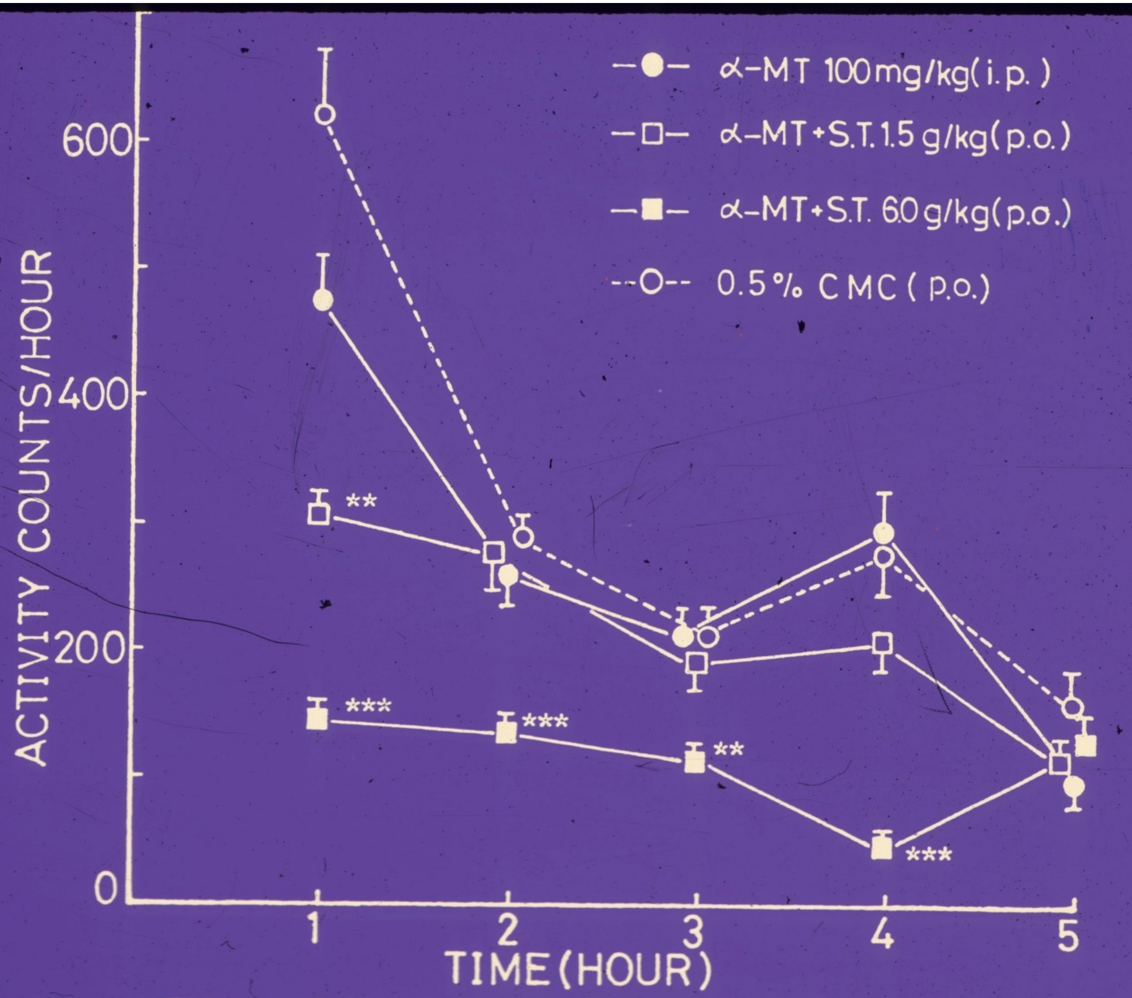


FIGURE 2 An idealized night's sleep in a normal young adult.



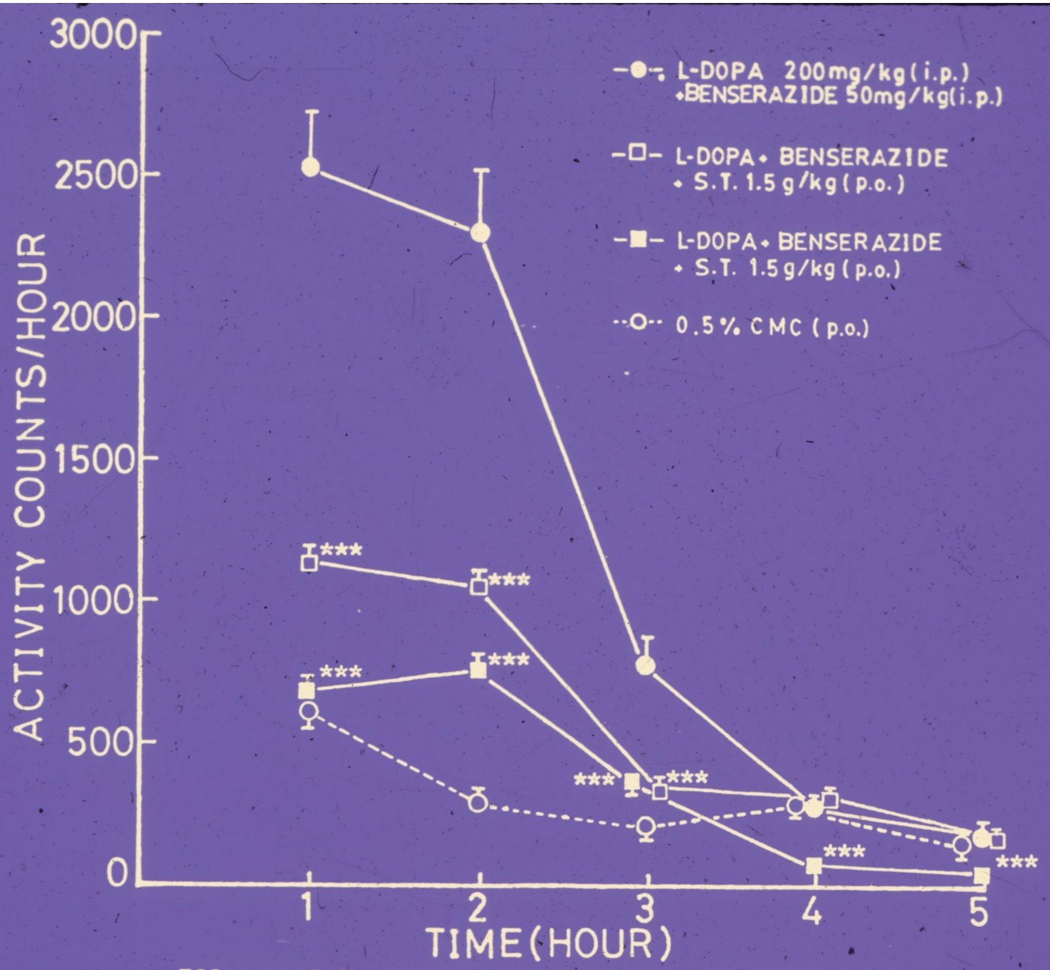
Effects of Suanzaorentang Ext. on the Locomotor Activity in Rats

* p<0.05 ** p<0.01 *** p<0.001



Effects of Suanzaorentang Ext. on changes in Locomotor Activity prduced by α-MT in Rats

** p<0.01 *** p<0.001



Effects of Suanzaorentang Ext. on changes in Locomotor Activity produced by L-DOPA plus benserazide in Rats

*** $p<0.001$

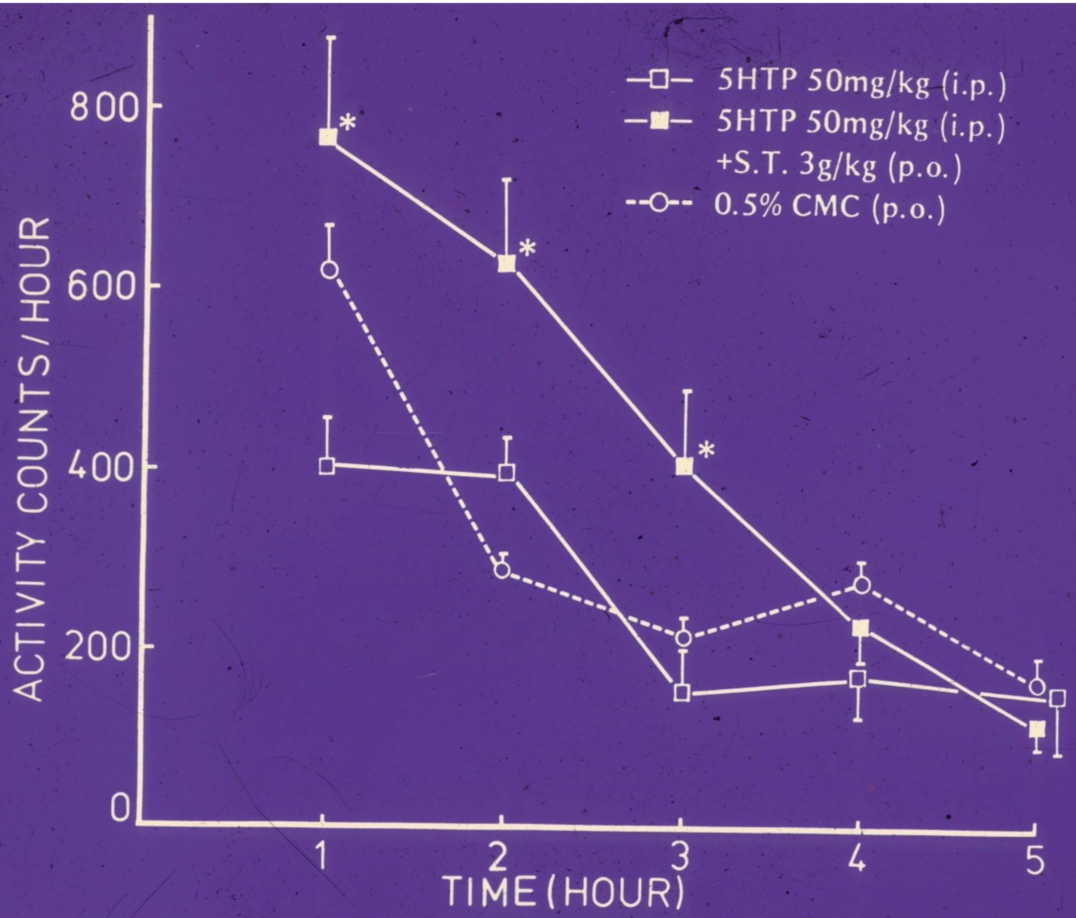


Fig. 1 Effects of Suanzaorentang on changes in Locomotor Activity produced by 5HTP in Rats
* $p < 0.05$

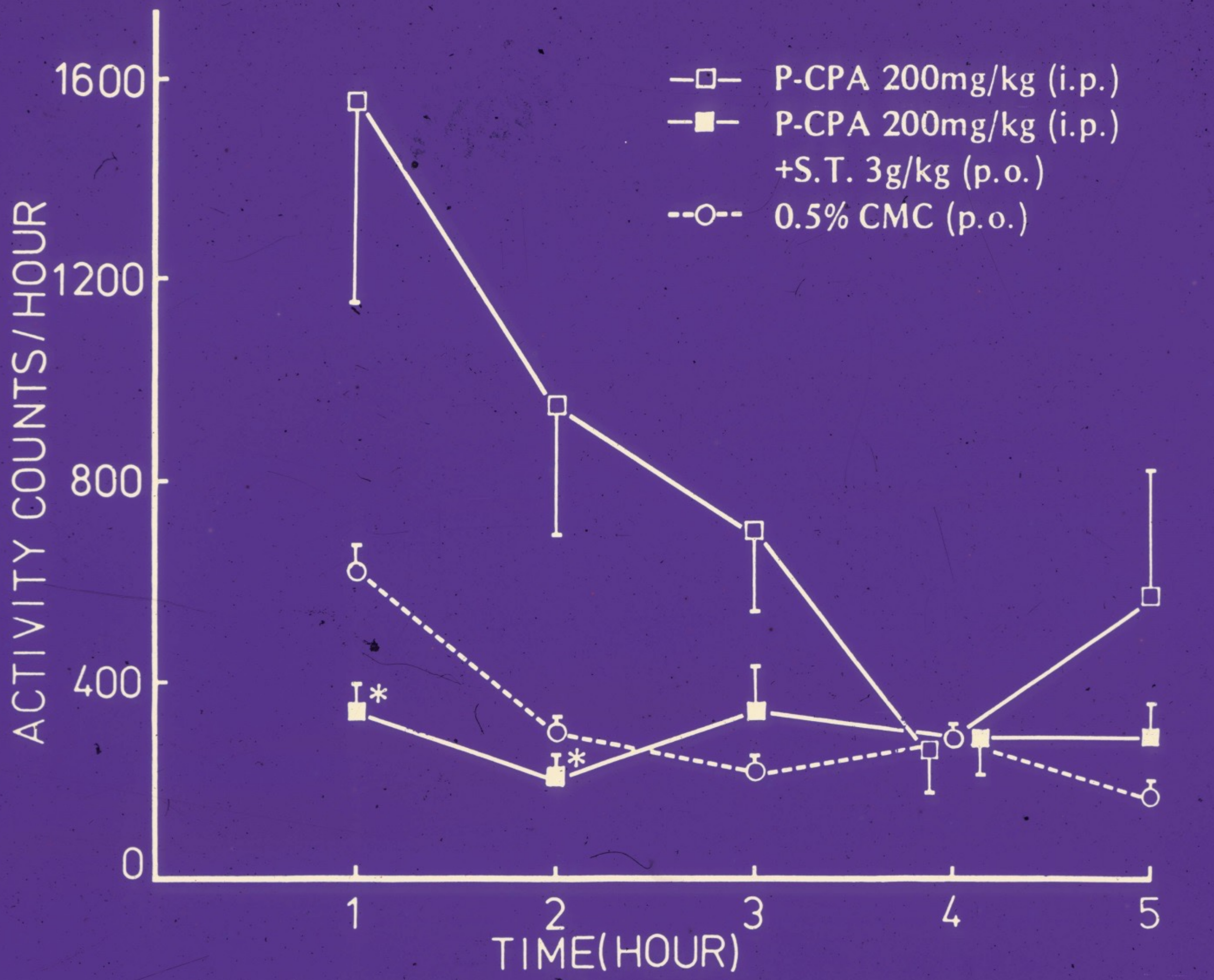


Fig. 2 Effects of Suanzaorentang on changes in Locomotor Activity produced by P-CPA in Rats

* $p < 0.05$

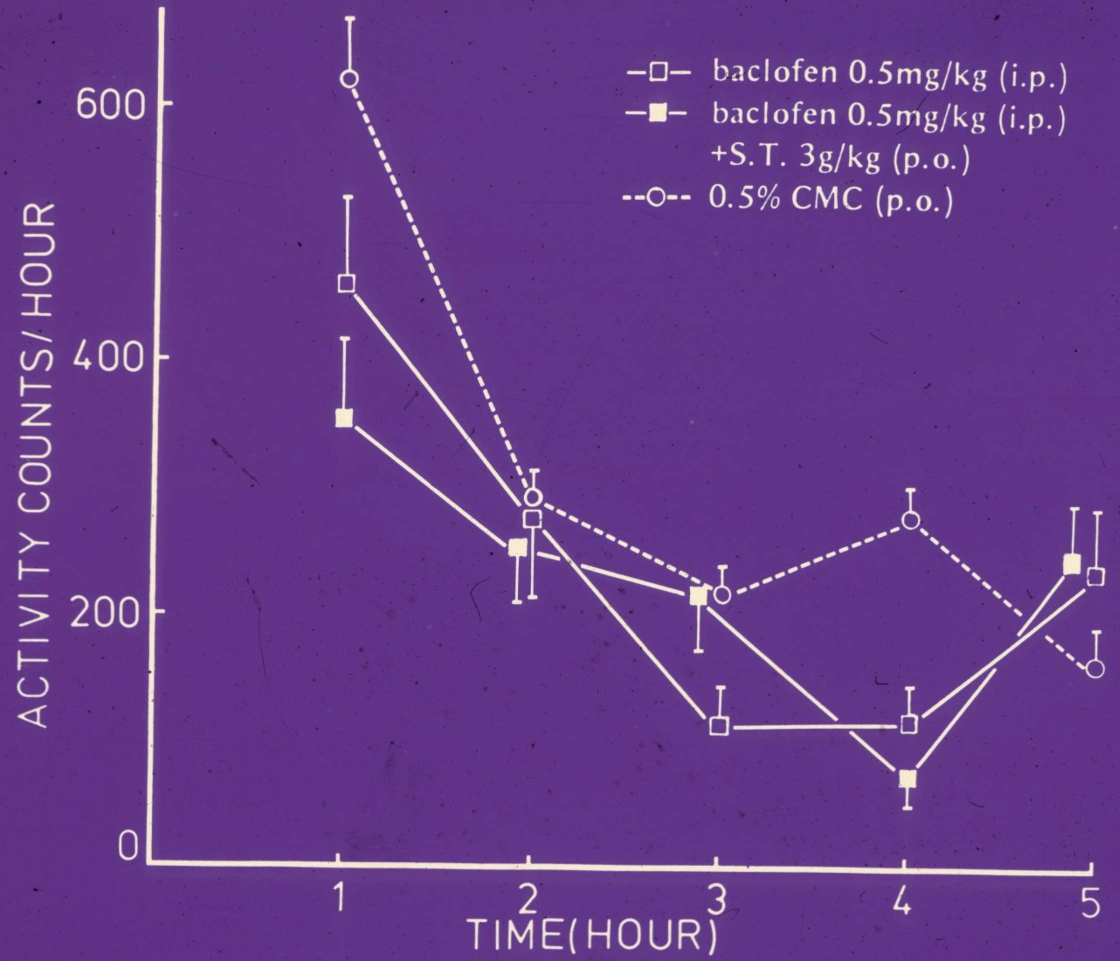


Fig. 3 Effects of Suanzaorentang on changes in Locomotor Activity produced by baclofen in Rats

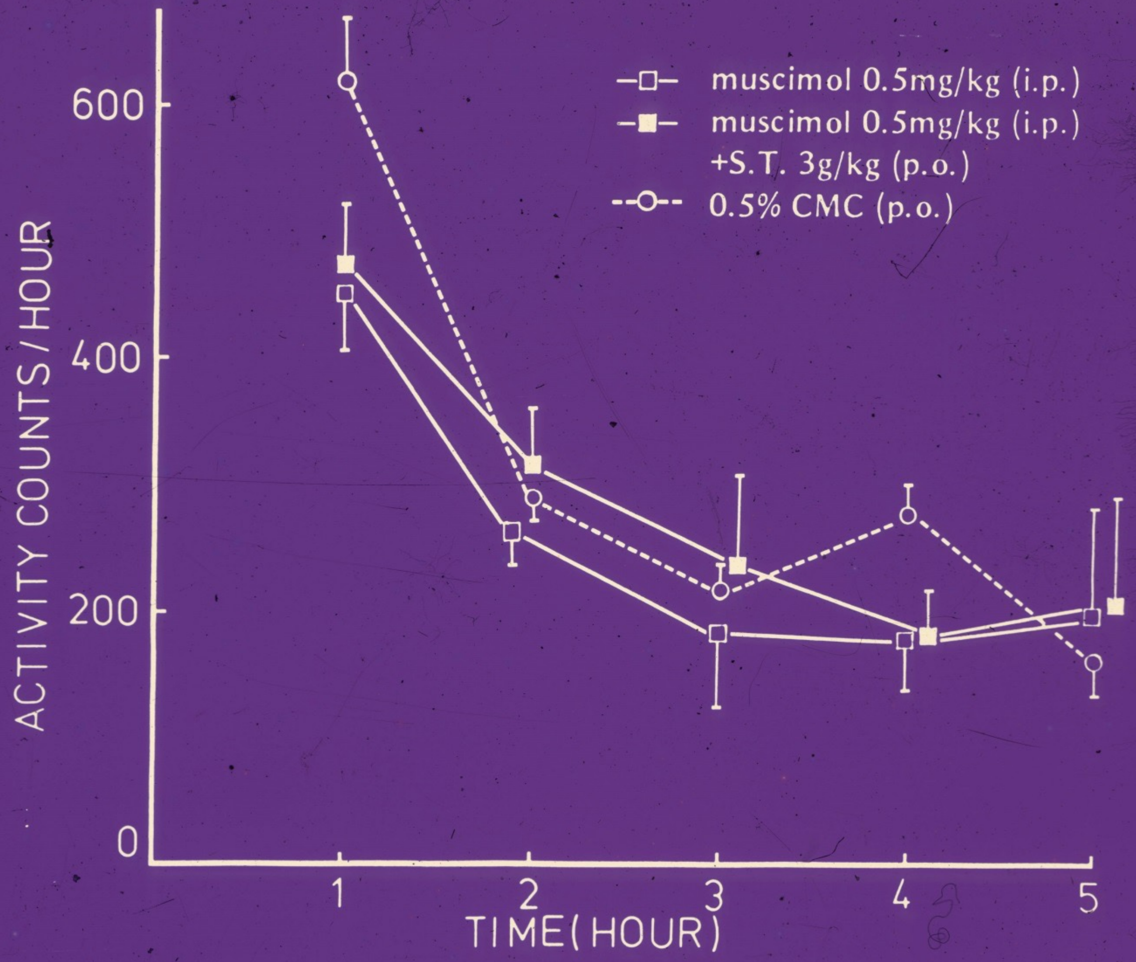


Fig. 4 Effects of Suanzaorentang on changes in Locomotor Activity produced by muscimol in Rats

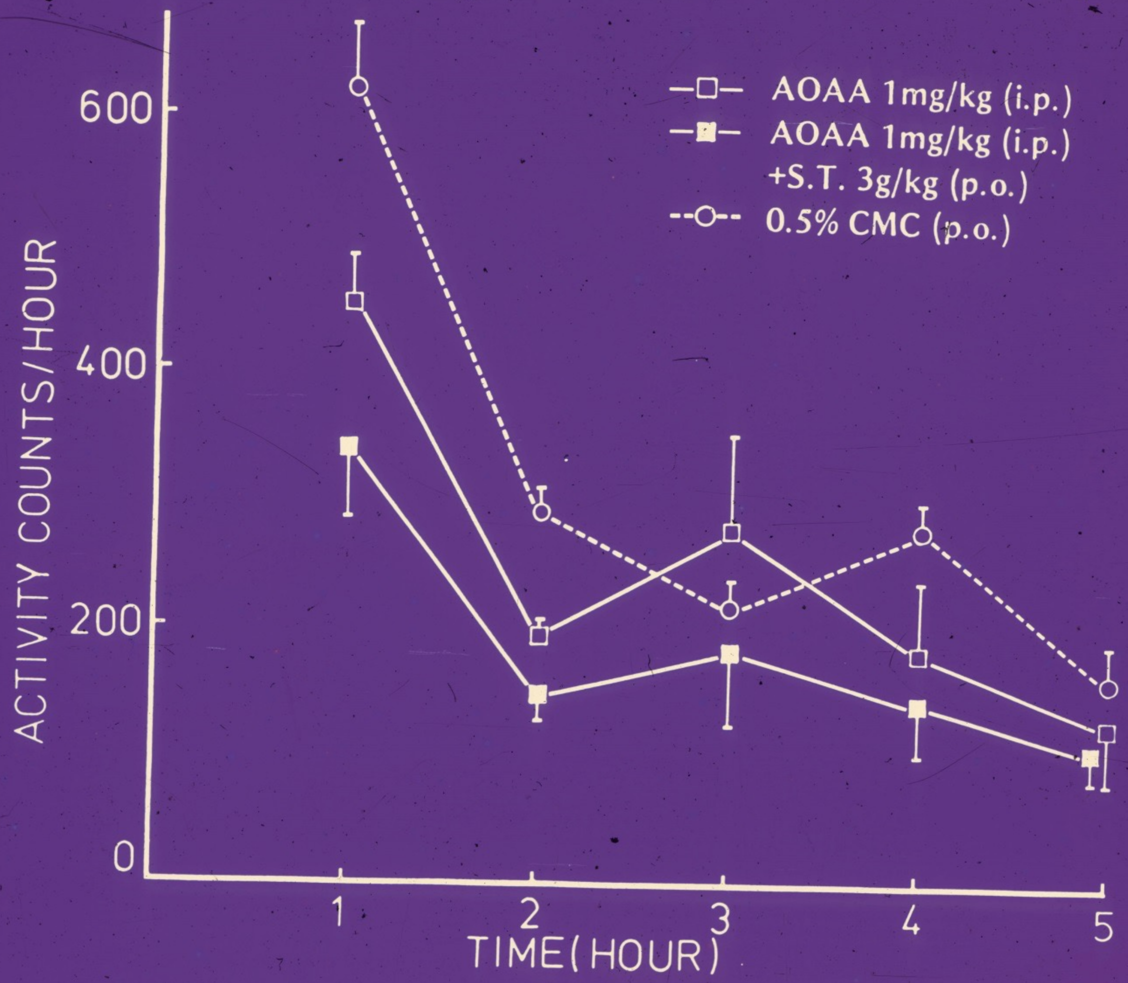


Fig. 5 Effects of Suanzaorentang on changes in Locomotor Activity produced by AOAA in Rats

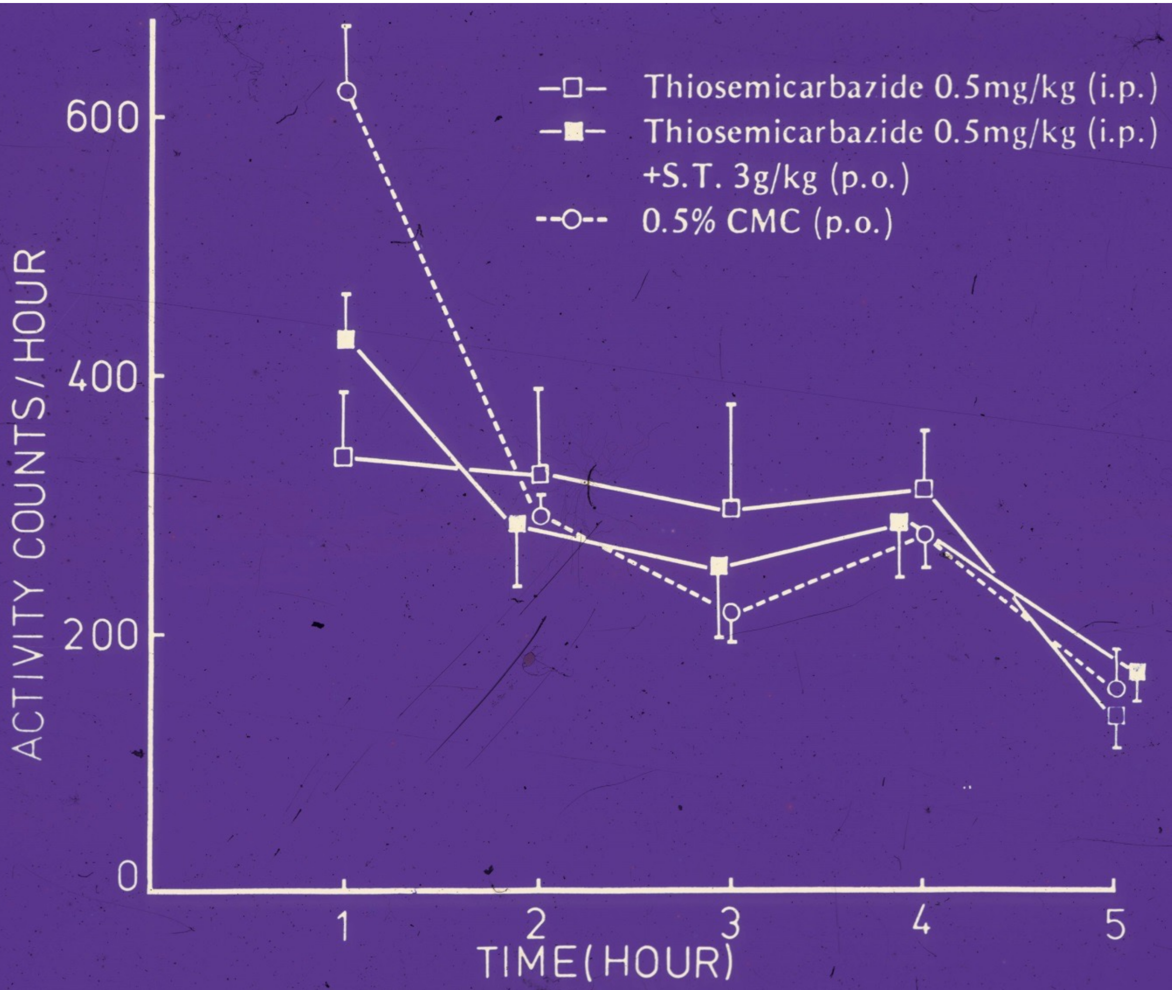
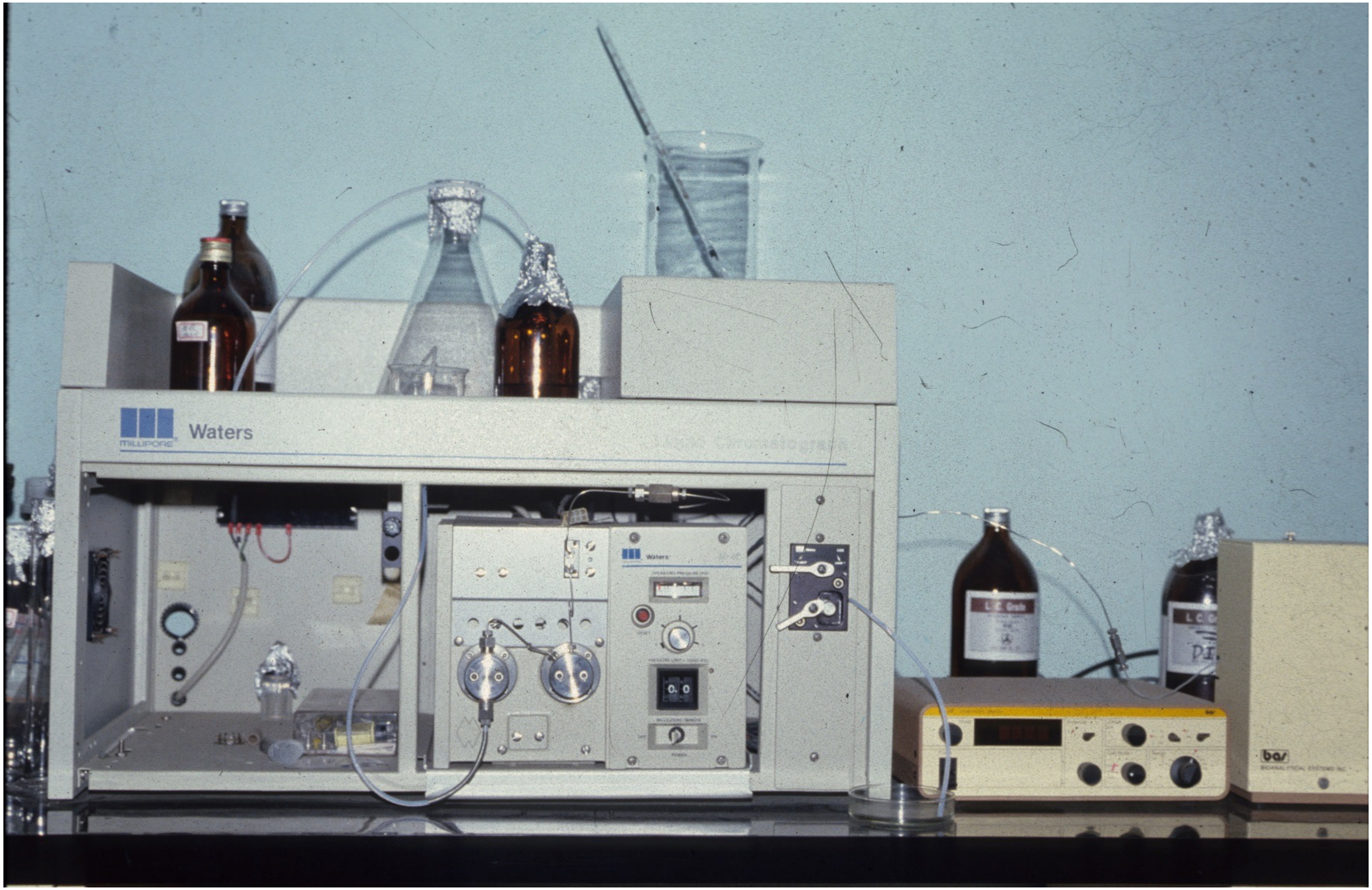
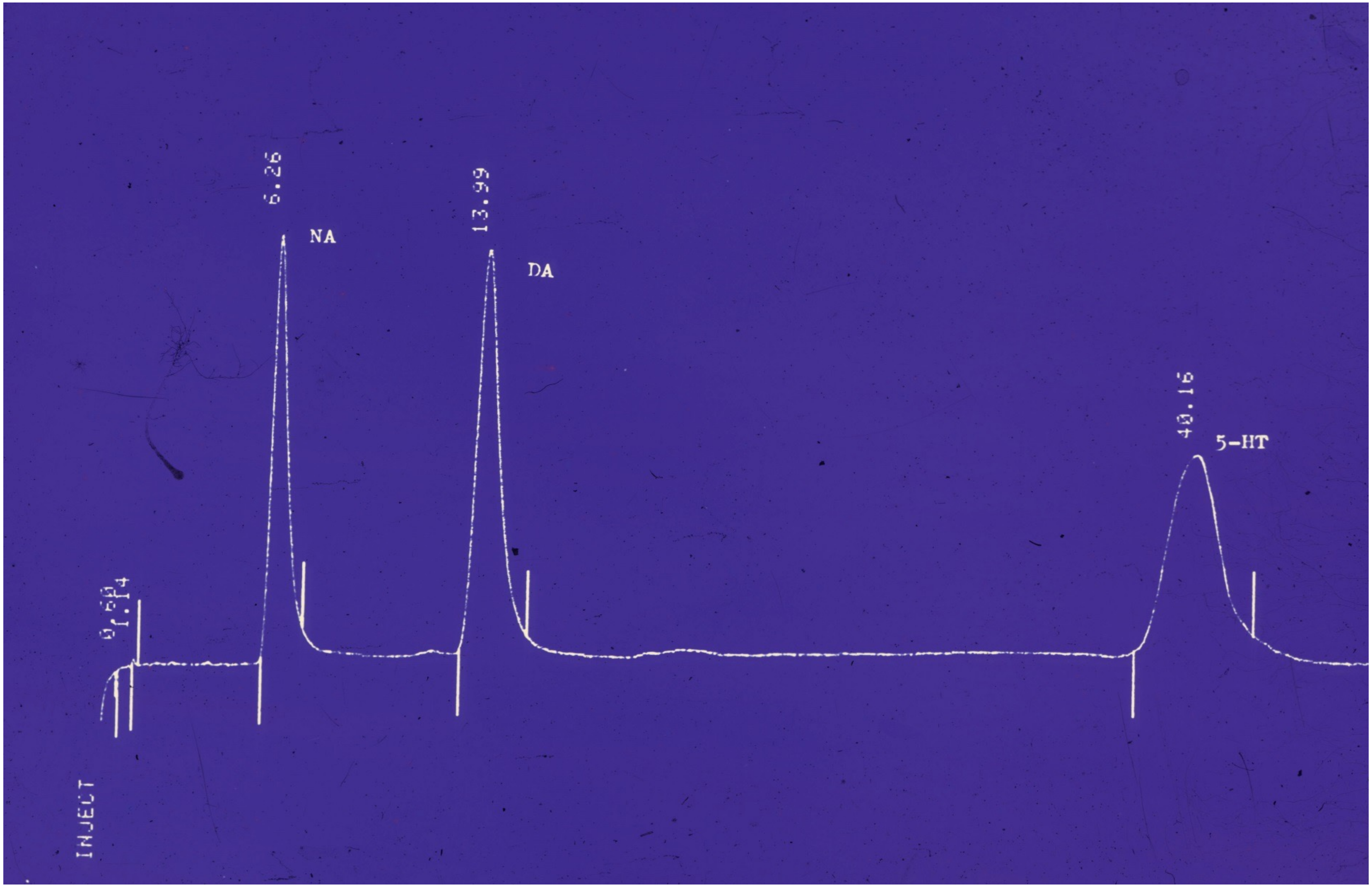
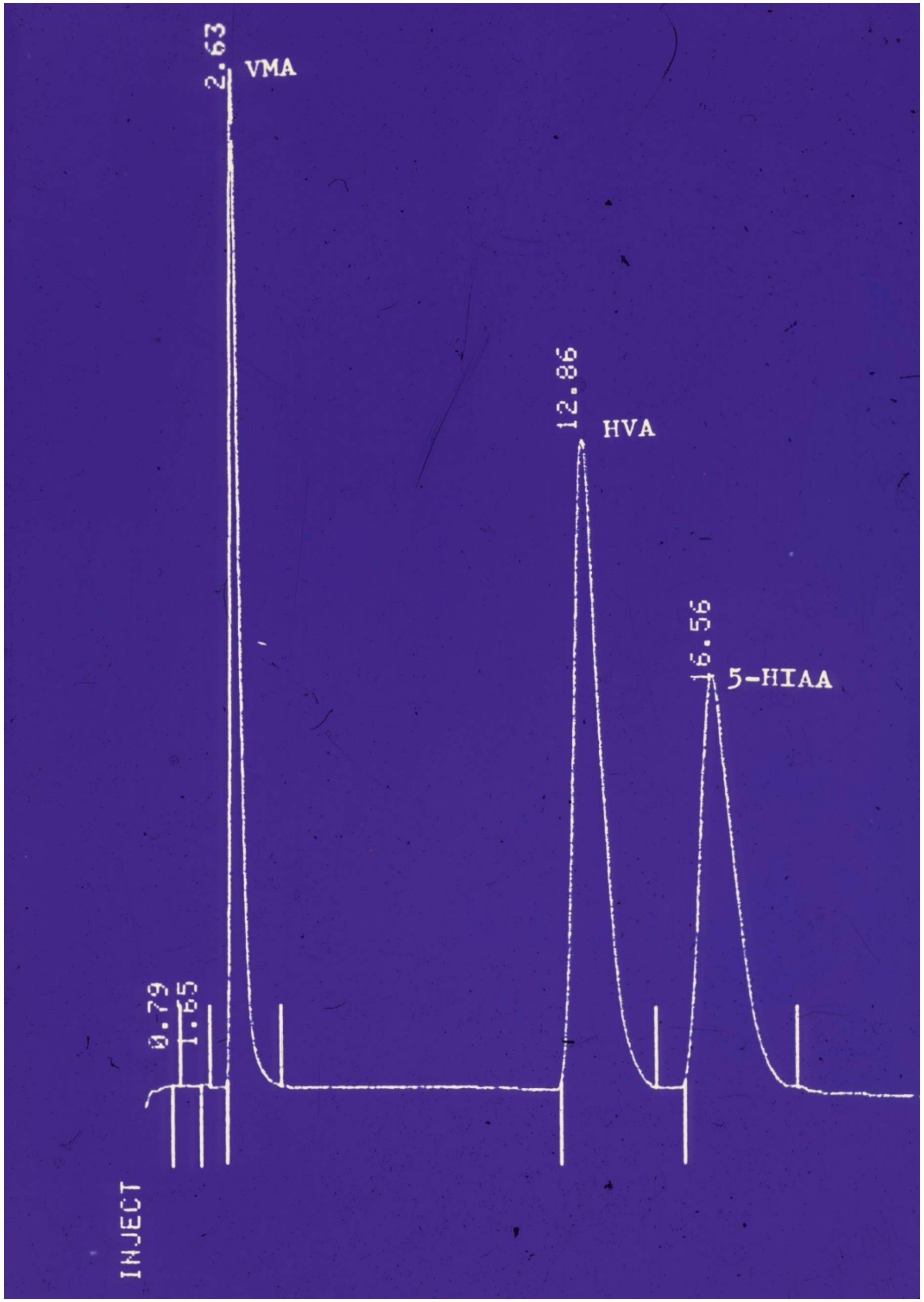


Fig. 6 Effects of Suanzaorentang on changes in Locomotor Activity produced by Thiosemicarbazide in Rats



MILLIPORE
Waters
Waters
bas


6.26
NA
13.99
DA
40.16
5-HT
0.50
1.14
INJECT



2.63
VMA
12.86
HVA
16.56
5-HIAA
0.79
1.65
INJECT

Table 1. Effects of Suanzaorentang (alcohol extracts) on monoamines and metabolites in various regions of the rat brain

		Cortex	Striatum	hippocampus	midbrain	hypothalamus	amygdalla	medulla oblongata	cerebellum
NA	Control	100.00±11.08	100.00±9.26	100.00±23.65	100.00±14.32	100.00±7.98	100.00±10.31	100.00±10.40	100.00±3.30
	S.T.	104.78±7.80	90.74±7.06	122.67±11.39	120.14±33.76	105.22±5.88	90.55±4.24	106.16±11.20	109.65±9.34
DA	Control	100.00±19.35	100.00±7.76	100.00±19.80	100.00±24.20	100.00±14.31	100.00±13.07	100.00±4.00	100.00±7.31
	S.T.	102.91±9.14	92.31±3.97	91.96±6.46	100.80±4.74	102.68±14.59	92.46±8.96	92.74±13.08	106.35±6.55
5-HT	Control	100.00±5.66	100.00±12.58	100.00±8.68	100.00±8.43	100.00±11.97	100.00±17.42	100.00±6.82	100.00±13.35
	S.T.	85.63±5.05	94.98±5.82	97.48±4.89	90.57±4.18	99.71±6.59	102.60±17.52	113.00±17.24	107.38±12.17
VMA	Control	100.00±6.62	100.00±6.82	100.00±9.73	100.00±14.38	100.00±7.31	100.00±12.49	100.00±11.40	100.00±8.45
	S.T.	98.35±12.94	61.05±4.87**	60.34±9.62*	97.21±16.91	109.53±11.20	93.29±10.06	93.86±7.51	108.76±12.10
5-HIAA	Control	100.00±10.09	100.00±8.40	100.00±2.53	100.00±11.89	100.00±14.42	100.00±11.99	100.00±9.38	100.00±10.76
	S.T.	74.57±5.19	51.29±7.53**	96.42±6.76	90.67±7.00	60.45±4.77*	103.77±14.35	96.24±11.22	98.31±7.55
HVA	Control	100.00±7.46	100.00±7.35	100.00±7.57	100.00±13.19	100.00±13.94	100.00±11.11	100.00±12.33	100.00±11.55
	S.T.	80.36±6.06	100.20±11.74	58.57±6.70**	94.15±11.08	100.60±12.66	104.37±12.14	101.25±4.53	93.59±8.44

Mean ± S.E. *$p < 0.05$

Control: 0.5% CMC **$p < 0.01$

S.T.: Suanzaorentang alcohol extracts 3.0 g/kg (p.o.)

Table 3. Effects of Suanzaorentang (alcohol extracts) on dopamine turnover in rat brain

DA / parts of brain	cortex	striatum	hippocampus	midbrain	hypothalamus	amygdalla	medulla oblongata	cerebellum
Control (0.5% CMC)	100.00±19.35	100.00±7.76	100.00±19.80	100.00±24.20	100.00±14.31	100.00±13.07	100.00±4.00	100.00±7.31
α-methyl-p-tyrosine (α-MT) 250mg/kg i.p.	71.72±6.62	60.13±4.56	49.40±4.99	72.04±7.75	65.93±8.64	69.59±6.55	68.95±8.90	66.21±7.20
α-MT 250mg/kg i.p. + S.T. 3g/kg p.o.	85.23±9.36	84.70±8.96*	78.70±7.90*	72.99±7.91	66.80±6.12	81.40±10.90	72.16±6.39	72.83±9.22

Mean ± S.E.
* $p < 0.05$

Table 2. Effects of Suanzaorentang (alcohol extracts) on noradrenaline turnover in rat brain

NA / parts of brain	cortex	striatum	hippocampus	midbrain	hypothalamus	amygdalla	medulla oblongata	cerebellum
Control (0.5% CMC)	100.00±11.03	100.00±9.26	100.00±23.65	100.00±14.32	100.00±7.98	100.00±10.31	100.00±10.40	100.00±3.30
α–methyl–p–tyrosine (α–MT) 250mg/kg i.p.	83.75±7.13	53.23±2.42	64.10±5.41	77.73±7.50	61.51±6.86	61.42±7.42	70.44±6.41	69.78±7.51
α–MT 250mg/kg i.p. + S.T. 3g/kg p.o.	92.75±11.33	61.68±6.56	68.94±4.10	84.18±7.80	68.12±10.34	67.68±5.13	76.88±10.64	75.33±10.92

Mean ± S.E.

Table 4. Effects of Suanzaorentang (alcohol extracts) on 5–hydroxytryptamine (5–HT) turnover in rat brain

5–HT / parts of brain	cortex	striatum	hippocampus	midbrain	hypothalamus	amygdalla	medulla oblongata	cerebellum
Control (0.5% CMC)	100.00±5.66	100.00±12.58	100.00±8.68	100.00±8.43	100.00±11.97	100.00±17.42	100.00±6.82	100.00±13.35
p–chlorophenylalanine (PCPA) 200mg/kg i.p.	65.35±7.85	63.56±6.67	63.89±5.63	69.58±5.23	70.84±9.21	62.75±8.45	70.11±4.62	74.85±10.90
PCPA 200mg/kg i.p. + S.T. 3g/kg p.o.	73.89±5.96	72.23±6.44	67.09±8.52	71.17±5.98	81.92±7.77	93.41±4.37*	77.81±5.89	79.66±7.08

Mean ± S.E.
*$p < 0.05$

酸棗仁湯對於大白鼠中樞腎上腺素及血清緊素系統之研究。

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SUANZAORENTANG, AN ANXIOLYTIC CHINESE MEDICINE, AFFECTS THE CENTRAL ADRENERGIC AND SEROTONERGIC SYSTEMS IN RATS.

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Zizyphus Combination

Suanzaorentang (S-T)

酸 棗 仁 湯

Ming-Tsuen Hsieh

謝 明 村

INTRODUCTION

(1) The ancient Chinese formula of Suanzaorentang (酸棗仁湯) was originally prescribed in Chin-Kuei-Yao-Lueh (金匱要略) for patients with insomnia.

(2) This research is to study the effects on behavioral pharmacology, including sedative and anticonvulsive action, and anti-insomnia effects of Suanzaorentang.

(3) This study will be divided into two groups:

1. Pharmacological studies.
2. Clinical studies.

The Components of the Suanzaorentang Formular are:

酸棗仁	Zizyphus spinosus Hu
茯苓	Poria cocos (Schw.) Wolf
芎藭	Ligusticum chuanxiong Hort.
知母	Anemarrhena asphodeloides Bunge
甘草	Glycyrrhiza uralensis Fischer et Dc.

Preparation of the Suanzaorentang

1. A mixture (1 kg) of coarse powders of Zizyphus spinosus Hu, Poria cocos (Schw.) Wolf, Ligusticum chuanxiong Hort, Anemarrhena asphodeloides Bunge and Glycyrrhiza uralensis Fischer et Dc. in the ratio of 7.5:2:2:1:1 was immersed in 5 liters 95% alcohol at room temperature for 3 days and then extracted in a water bath.
2. The extracted solution was evaporated and concentrated in a rotary vacuum evaporator.
3. The sample was obtained by lyophilizing the concentrated extract and then pulverizing through a No.80# mesh.

PHARMACOLOGICAL STUDIES

1. Observe naive behavior.
2. The effects on hexobarbital induced sleeping time.
3. The effects on chemically induced convulsive seizures.
4. The effects on locomotor activity changes produced by various substances which may influence the monoaminergic and GABAergic systems.
5. The effects on the concentrations monoamines in different parts of the brain in rats.

ANIMALS

1. Male Sprague-Dawley rats, weighing about 200 g, were used in the studies of locomotor activity and the concentration of brain monoamines.
2. Male ICR mice, weighing about 20 g, were used in the studies of drug-induced convulsions and drug-induced sleep.

DRUG AND TREATMENT REGIMENS

1. The following compounds were used:

   (1) Tyrosine hydroxylase inhibitor:

   α-methyl-p-tyrosine (α-MT)

   (2) Dopamine precursor: Levodopa

   (3) Decarboxylase inhibitors: Benserazide

   (4) Serotonin precursor: 5-HTP

   (5) Serotonin synthesis inhibitor: p-CPA

   (6) GABA agonist: Baclofen, Muscimol

   (7) GABA transaminase inhibitor: AOAA

   (8) GABA antagonist: thiosemicarbazide

   (9) Analeptic stimulants:

   Strychnine, Picrotoxin, Pentylenetetrazol

   (10) Hypnotics: hexobarbital

2. Control rats or mice were given 0.5% CMC solution by p.o. route.

1. Effects of Suanzaorentang on drug induced convulsions:

   The time period to produce clonic convulsion (C.C.) and the time period between clonic and tonic convulsion (T.C.) by gross observation were used as the indices of the effects of Suanzaorentang on drug induced convulsions.

2. Effects of Suanzaorentang on drug-induced sleep:

   Sleep time was recorded as the time period between the loss and the recovery of the righting reflex.

Table 2. Effects of S-T on Pentylenetetrazol-, Picrotoxin-, and Strychnine-Induced Convulsions in Mice

Dose (g/kg)	Pentylenetetrazol		Picrotoxin		Strychnine	
	C.C. (min)	T.C. (min)	C.C. (min)	T.C. (min)	T.C. (min)	Time for death (min)
Control	0.61±0.03	3.03±0.28	6.23±0.17	5.67±0.41	2.48±0.22	2.82±0.25
1.5	0.64±0.03	4.06±0.42	6.22±0.25	5.41±0.45	2.25±0.23	2.65±0.22
3.0	0.66±0.03	5.04±0.37*	7.12±0.20*	6.31±0.26	2.35±0.20	2.91±0.19
6.0	0.66±0.03	6.19±0.52*	7.81±0.40*	8.85±0.42*	2.10±0.26	2.63±0.24

1. C.C.: The time to produce clonic convulsion.
2. T.C.: From clonic to tonic convulsions.
3. Suanzaorentang significantly prolonged the period from clonic to tonic convulsions by pentylenetetrazol.
4. Suanzaorentang significantly prolonged C.C. and T.C. by picrotoxin.
5. Suanzaorentang did not inhibit the strychnine-induced convulsion.

*$P < 0.05$ (compared to controls)

$n = 10$, mean ± S.E.

Table 1. Effect of S-T on Hexobarbital-Induced Sleep in Mice

Dose (g/kg)	Onset (min)	Sleep (min)
Control	8.41±0.50	37.70±2.79
1.5	7.72±0.46	51.00±2.91*
3.0	6.96±0.25	74.80±4.40*
6.0	6.57±0.22	85.10±6.96*

1. Onset: The time to produce disappearance of righting reflex
2. Sleep time: From the loss to the recovery of righting reflex
3. Suanzaorentang significantly potentiated the hypnotic effect of hexobarbital.

*$p < 0.05$ (compared to control)

n = 10, mean ± S.E.

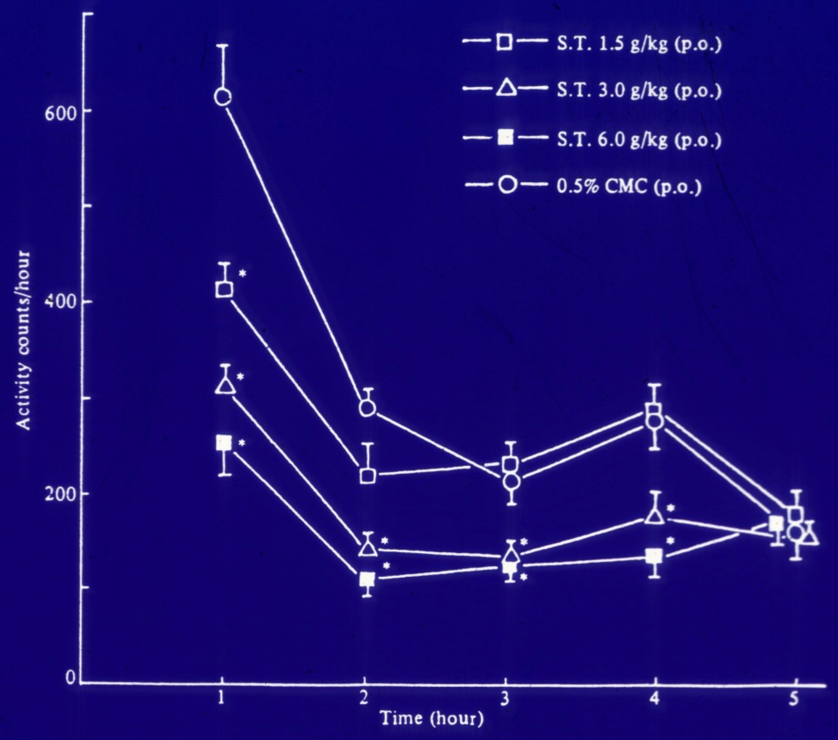


Figure 1. 1. Effects of Suanzaorentang on the locomotor activity in rats.

2. Rats treated with S-T exhibited a significant decrease on locomotor activity in a dose-dependent.

Pathway of metabolism of catecholamines

phenylalanine

↓ hydroxylase

tyrosine

α-MT - - - → ↓ tyrosine hydroxylase

dopa

↓ amino decarboxylase

dopamine (DA) —MAO→ —COMT→ 3-methoxy-4-hydroxy phenylacetic acid (HVA)

↓ dopamine β-hydroxylase

Norepinephrine (NE) —COMT→ —MAO→ 3-methoxy-4-hydroxy mandelic acid (VMA)

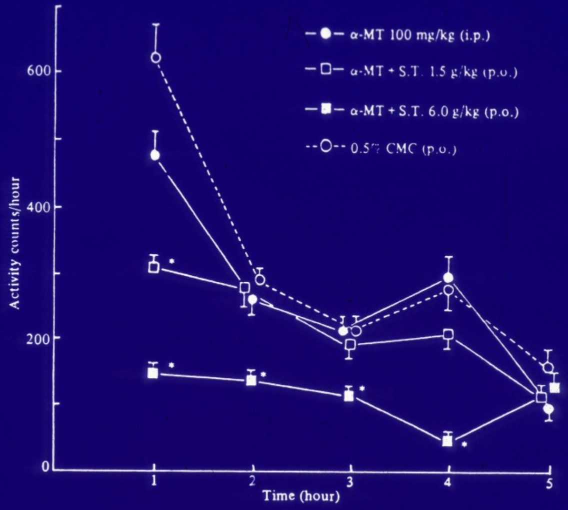


Figure 2. 1. Effects of Suanzaorentang on changes in locomotor activity produced by α-MT in rats.

2. Rats pretreated with α-MT appeared to be behaviorally depressed as compared with the 0.5% CMC control.

3. The hypomotility produced by α-MT was significantly augmented by S-T.

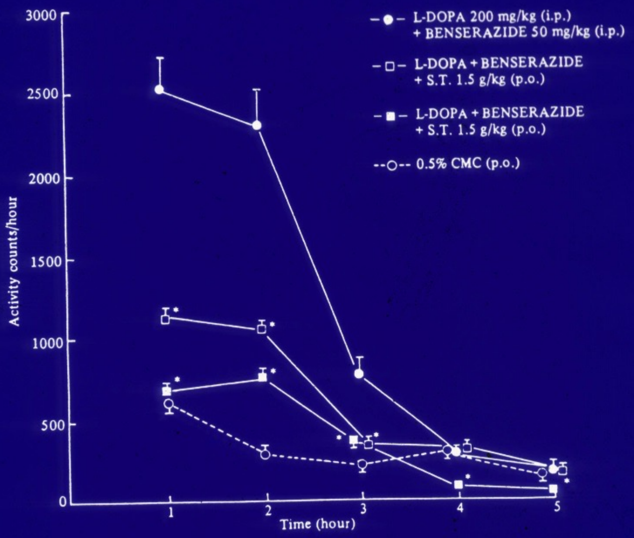


Figure 3. 1. Effects of Suanzaorentang on changes in locomotor activity produced by levodopa plus benserazide in rats.

2. Levodopa plus benserazide produced a significant increase in locomotor activity.

3. Locomotor stimulation was strongly reduced by S-T.

Pathway of metabolism of 5-hydroxytryptamine

tryptophan

P-CPA - - - → ↓ tryptophan hydroxylase

5-hydroxytryptophan (5-HTP)

↓ ℓ-amino acid decarboxylase

5-hydroxytryptamine (5-HT)

↓ monoamine oxidase

5-hydroxyindoleacetaldehyde

↓ aldehyde dehydrogenase

5-hydroxyindoleacetic acid (5-HIAA)

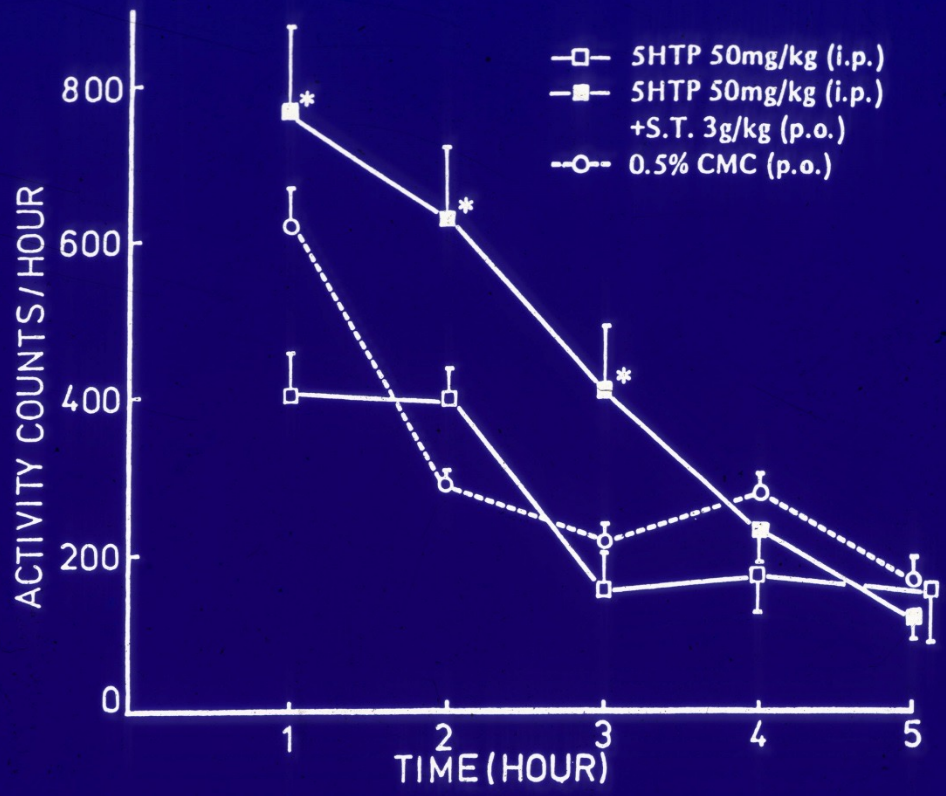


Figure 4. 1. Effects of Suanzaorentang on changes in locomotor activity produced by 5-HTP in rats.

2. 5-HTP induced decrease in locomotor activity was significantly antagonized by S-T.

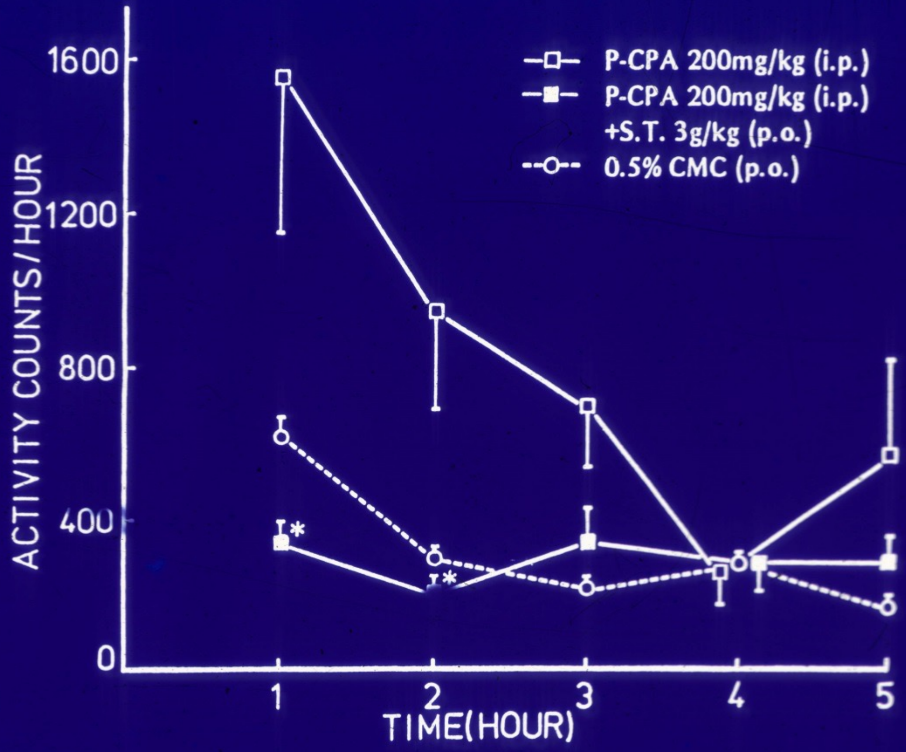


Figure 5. 1. Effects of Suanzaorentang on changes in locomotor activity produced by p-CPA in rats.

2. p-CPA induced increase in locomotor activity was significantly inhibited by S-T.

Pathway of metabolism of GABA

Glutamic acid

TSC - - - - → ↓ glutamate decarboxylase

α-aminobutyric acid (GABA)

AOAA - - - - → ↓ transaminase

Succinic semialdehyde

↓ dehydrogenase

α-hydroxybutyric acid (GHB)

↓ cyclization

α-butyrolactone (GBL)

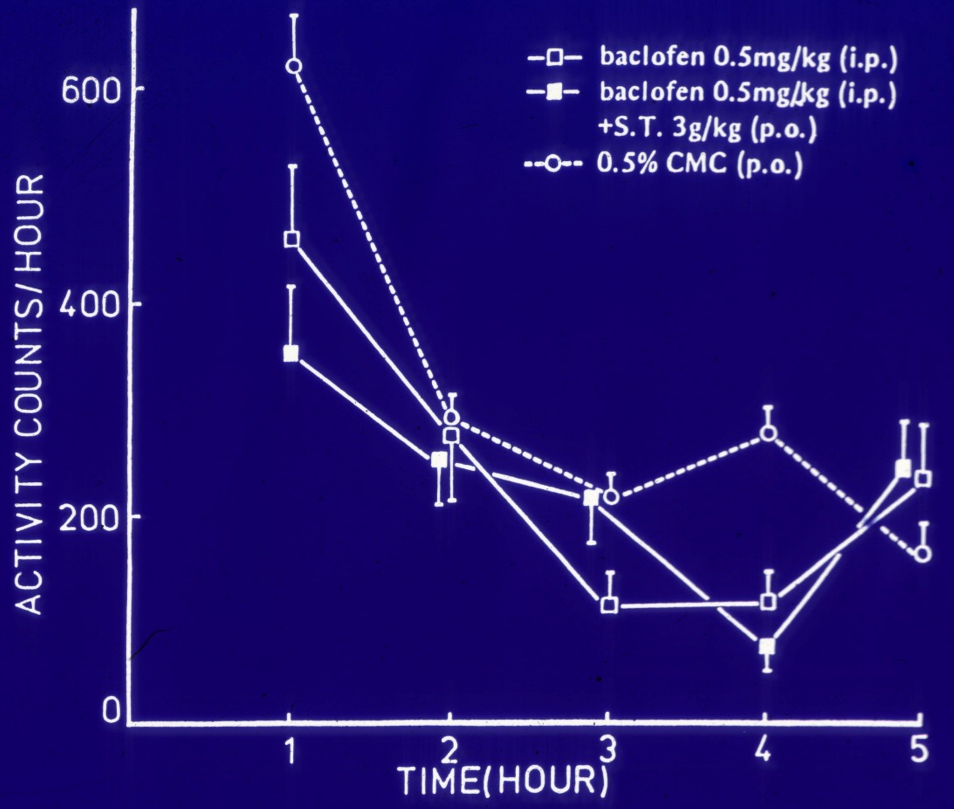


Figure 6. 1. Effects of Suanzaorentang on changes in locomotor activity produced by baclofen in rats.
2. S-T had no significant effect on baclofen induced changes in locomotor activity.

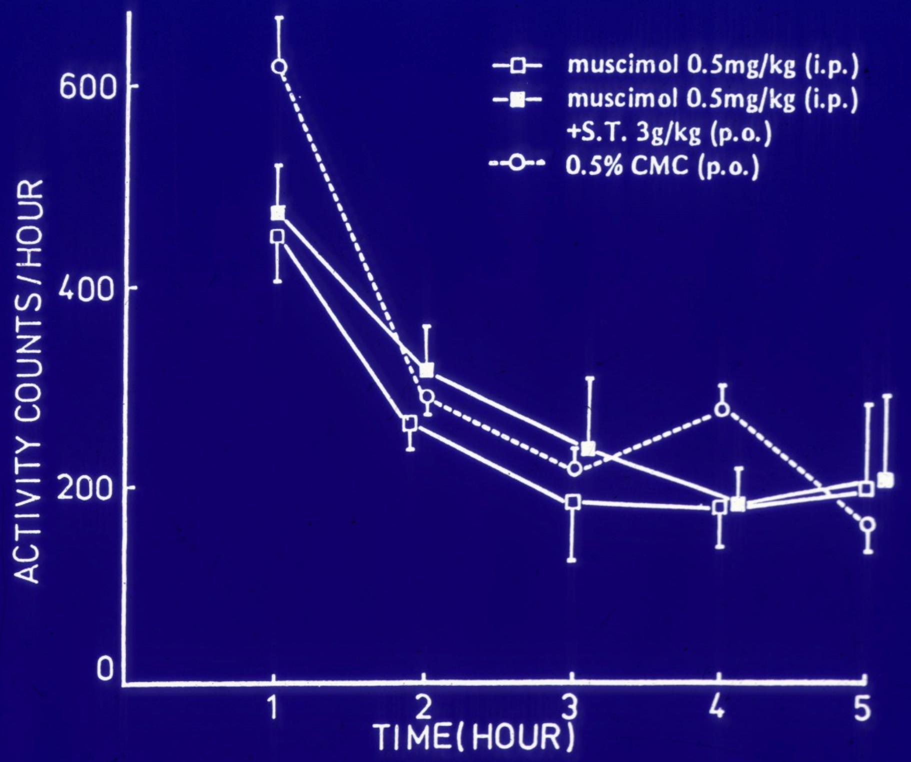


Figure 7. 1. Effects of Suanzaorentang on changes in locomotor activity produced by muscimol in rats.
2. S-T had no significant effect on muscimol induced changes in locomotor activity.

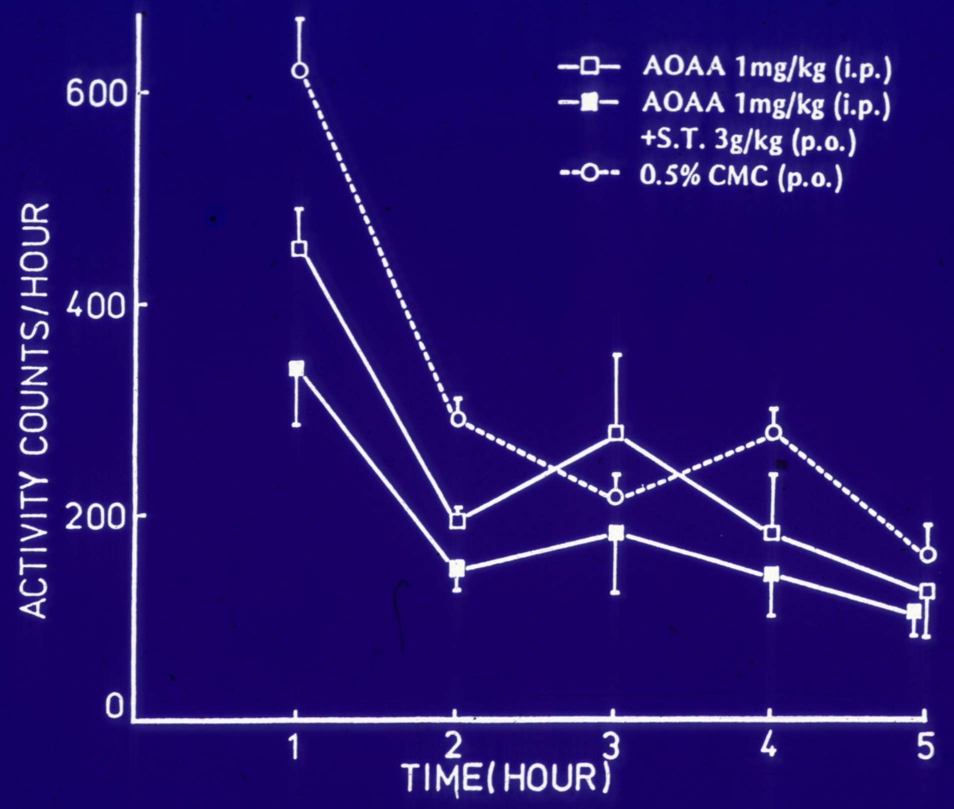


Figure 8. 1. Effects of Suanzaorentang on changes in locomotor activity produced by AOAA in rats.

2. S-T had no significant effect on AOAA induced changes in locomotor activity.

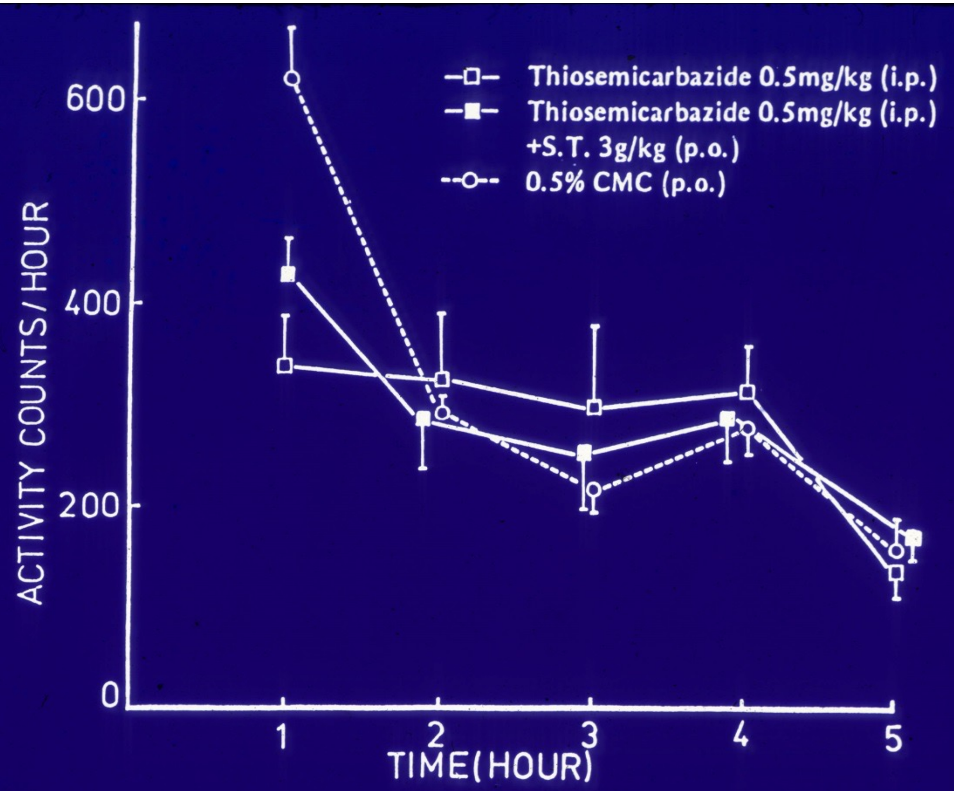


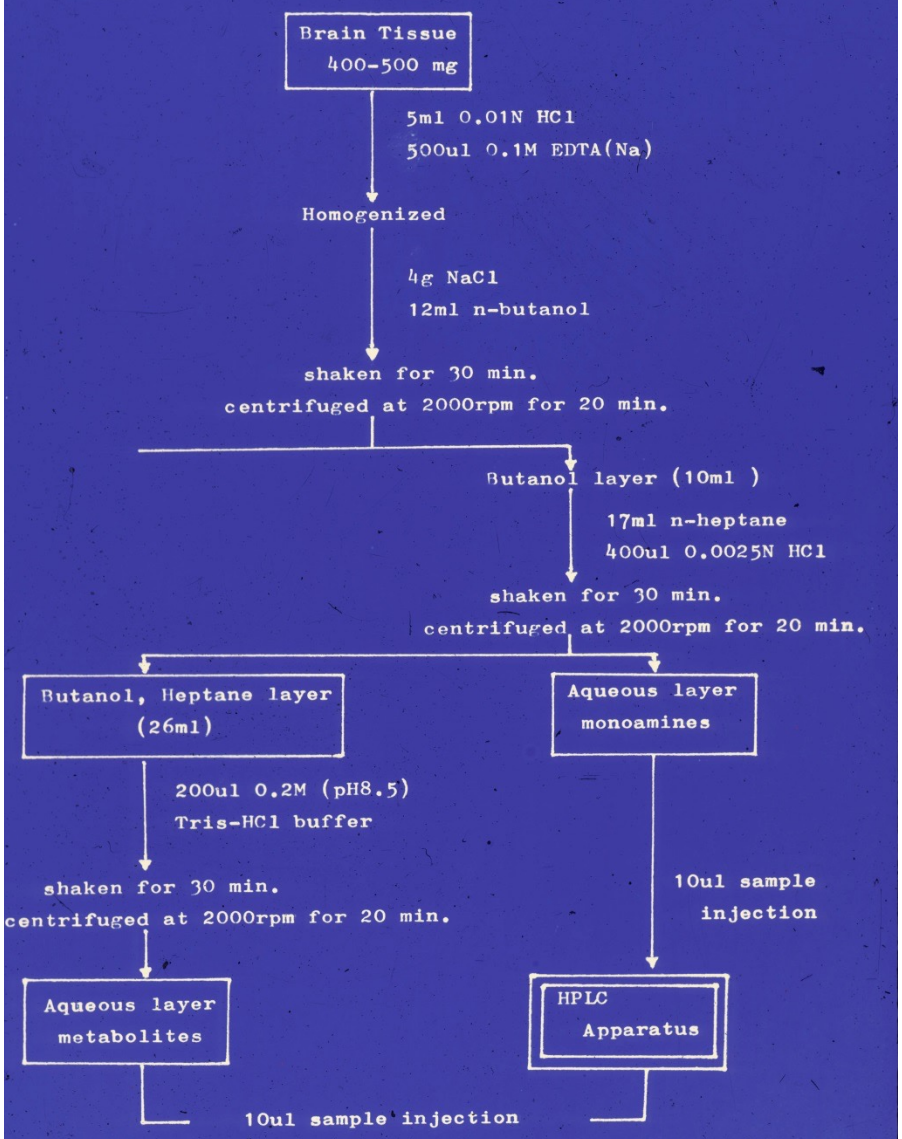
Figure 9. 1. Effects of Suanzaorentang on changes in locomotor activity produced by thiosemicarbazide in rats.

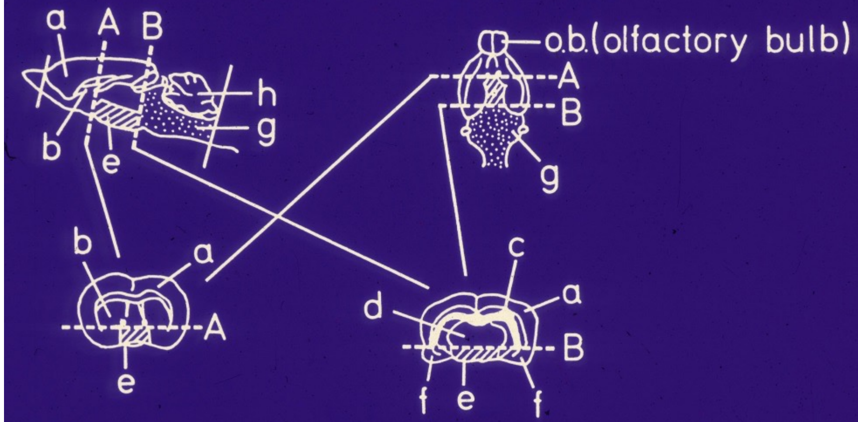
2. S-T had no significant effect on thiosemicarbazide induced changes in locomotor activity.

Effects of Suanzaorentang on the Concentration of Brain Monoamines-Metabolites in Rats

1. The concentrations of 5-HT, DA, NE and their metabolites were measured by HPLC with Electrochemical Detector.
2. The whole brain was separated into the following 8 parts according to the method of Glowinski: cortex, striatum, hippocampus, midbrain, hypothalamus, amygdala, medulla oblongata and cerebellum.

BRAIN TISSUE CLEANUP METHOD BEFORE HPLC BIOGENIC MONOAMINE AND METABOLITE ANALYSIS





a. cortex

b. striatum

c. hippocampus

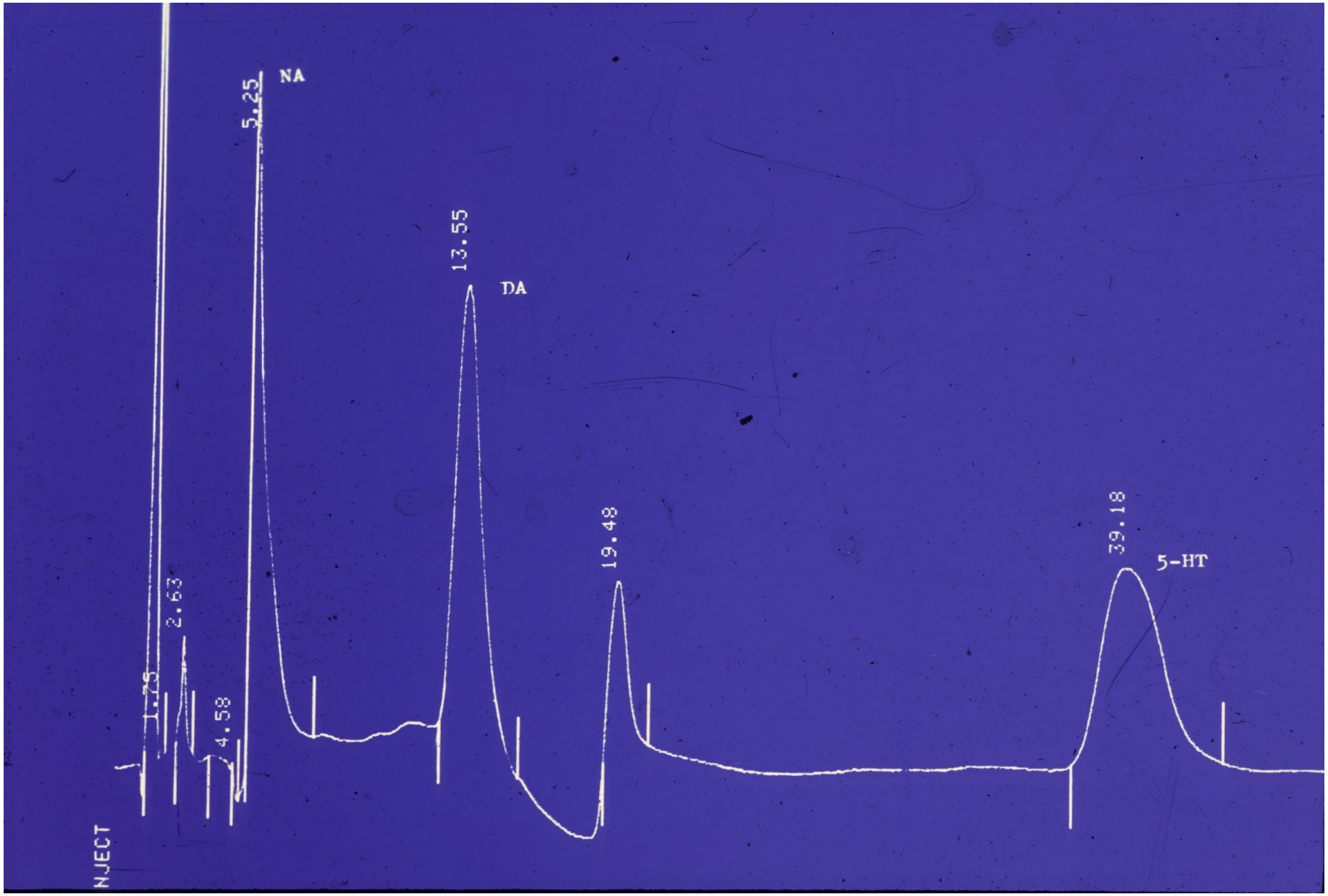
d. midbrain (thalamus)

e. hypothalamus

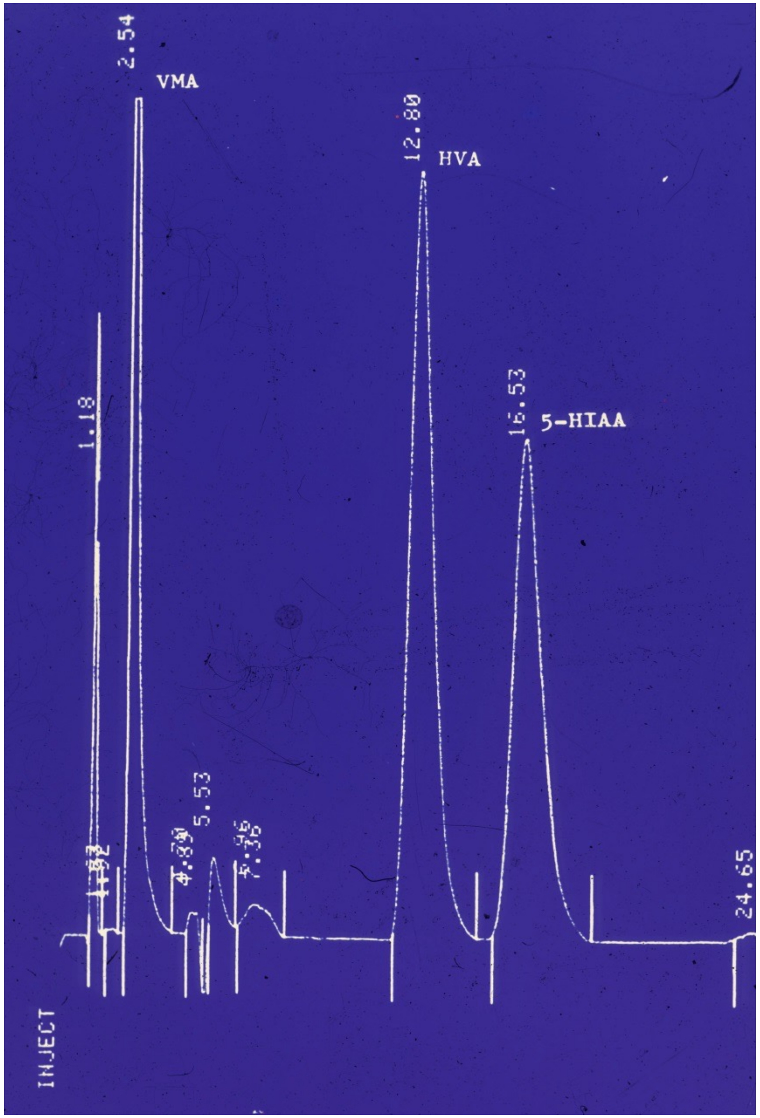
f. amygdalla (temporal part including amygdalla)

g. medulla oblongata (lower brainstem)

h. cerebellum



NA
5.25
13.55
DA
19.48
39.18
5-HT
1.75
2.63
4.58
NJECT



2.54
VMA
12.80
HVA
16.53
5-HIAA
1.18
5.53
24.65
INJECT

Table 3. Effects of Suanzaorentang (alcohol extracts) on monoamines and metabolites in various regions of the rat brain

		Cortex	Striatum	hippocampus	midbrain	hypothalamus	amygdala	medulla oblongata	cerebellum
NA	Control	1151±130	1870±170	1550±370	1420±200	1460±120	1680±170	1450±150	1390±50
	S.T.	1210±90	1700±130	1900±180	1710±480	1530±90	1520±70	1540±160	1520±130
DA	Control	1160±230	1620±130	1490±300	1430±350	1600±230	1460±190	1350±50	1410±100
	S.T.	1200±110	1490±60	1370±100	1450±70	1640±230	1350±130	1250±180	1490±90
5-HT	Control	1370±80	1620±200	1360±120	1640±140	1500±180	1430±250	1460±100	1190±160
	S.T.	1170±70	1540±90	1330±70	1490±70	1490±100	1460±250	1460±250	1280±150
VMA	Control	427±28	1530±100	1460±140	575±83	582±43	526±66	533±61	505±43
	S.T.	420±55	935±75**	882±141*	559±97	638±65	491±53	501±40	549±61
HVA	Control	940±71	916±67	1370±100	635±84	537±75	546±61	542±67	501±59
	S.T.	756±57	918±108	805±92**	598±70	540±68	569±66	549±25	477±43
5-HIAA	Control	562±57	1250±100	1500±40	740±88	688±99	575±69	530±49	502±54
	S.T.	419±29	639±94**	1440±100	671±52	416±33*	596±82	510±59	493±38

1. Mean ± S.E. (n = 5)
2. *p< 0.05, **p< 0.01 as analyzed by unpaired comparison Student's-t-test
3. Control: 0.5% CMC, S.T.: Suanzaorentang alcohol extracts 3.0g/kg (p.o.)
4. S.T. is compared to control (0.5% CMC)
5. S.T. had no significant effects on monoamines (5-HT, NA, DA) in the 8 parts of the rat brain.
6. S.T. significantly decreased VMA in striatum and hippocampus, HVA in hippocampus, 5-HIAA in striatum and hypothalamus.

Table 4. Effects of Suanzaorentang (alcohol extracts) on dopamine turnover in rat brain

DA / parts of brain	cortex	striatum	hippocampus	midbrain	hypothalamus	amygdala	medulla oblongata	cerebellum
Control (0.5% CMC)	1160±230	1620±130	1490±300	1430±350	1600±230	1460±190	1350±50	1410±110
α-methyl-p-tyrosine (α-MT) 250mg/kg i.p. + CMC	834±77	971±74	737±75	1030±110	1050±140	1020±100	929±120	930±101
α-MT 250mg/kg i.p. + S.T. 3g/kg p.o. + CMC	991±109	1370±140*	1170±120*	1050±110	1070±100	1190±160	973±86	1020±130

1. Mean + S.E. (n = 5)
2. DA concentrations are in ng/g wet weight
3. *$p < 0.05$ as analyzed by unpaired comparison of Student's-t-test
4. α-MT + S.T. + CMC is compared to α-MT + CMC
5. S.T. significantly reversed the α-MT produced decrease in DA concentrations in striatum and hippocampus

Table 5. Effects of Suanzaorentang (alcohol extracts) on 5-hydroxytryptamine (5-HT) turnover in rat brain

5-HT / parts of brain	cortex	striatum	hippocampus	midbrain	hypothalamus	amygdala	medulla oblongata	cerebellum
Control (0.5% CMC)	1370±80	1620±200	1360±120	1640±140	1500±180	1430±250	1460±100	1190±160
p-chlorophenylalanine (PCPA) 200mg/kg i.p. + CMC	892±107	1030±110	870±77	1140±90	1060±140	895±120	1020±70	893±130
PCPA 200mg/kg i.p. + S.T. 3g/kg p.o. + CMC	1010±80	1170±100	913±116	1170±100	1230±120	1330±60*	1130±90	950±84

1. Mean + S.E. (n = 5)

2. 5-HT concentrations are in ng/g wet weight

3. *$p < 0.05$ as analyzed by unpaired comparison of Student's-t-test

4. p-CPA + S.T. + CMC is compared to p-CPA + CMC

5. S.T. significantly reversed the p-CPA produced decrease in 5-HT concentrations in amygdala.

Studies on the Suanzaorentang in the treatment of anxiety and insomnia

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Ming-Tsuen Hsieh

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Taiwan , R.O.C.

Studies on the Suanzaorentang in the Treatment of Anxiety and Insomnia

PROTOCOL

Placebo S-T(250 mg, t.i.d.) Placebo

Diazepam(2 mg, t.i.d.)

1 week 1 week

Anxiety measure Anxiety measure

(1) In the 1st week, a placebo made of lactose was given. Patients started on three capsules per day.

(2) The anxiety and psychomotor measures were made before and after the 1st week of placebo.

(3) After the 1st week S-T was given, after 1 week the anxiety and psychomotor measures were carried out again.

CLINICAL STUDIES

1. Choice of Patients:

   (1) Insomnia or anxiety patients without organic causes.

   (2) To randomize the sampling, the presenting sampling technique will be used.

   (3) Ages: 20 years-60 years.

   (4) Sex: Evenly distributed in both sexes.

   (5) Patients meeting the criteria set by the American Psychiatic Association will be chosen as our potential subjects to study the antianxiety effects of Suanzaorentang.

CLINICAL STUDIES

2. Patients Meeting All the Following Criteria Were Selected as Our Subjects:

   (1) Patients with symptoms and signs of sympathetic hyperactivity, motor hypertonicity and apprehension.

   (2) Patients with Morbid Anxiety Inventory (MAI) score between 14 and 30.

   (3) Patients without other specific conditions (for example: heart failure, hypertension), not pregnant and not taking any medication in the previous 2 weeks.

CLINICAL STUDIES

3. Evalution of the Therapeutic Effects:

   (1) Anti-insomnia effect.

   (2) The antianxiety effects will be evaluated by the Hamilton Anxiety Scale and Morbid Anxiety Inventory.

   (3) The psychomotor effect will be evaluated by the Digital Symbol Substitution Test.

Table 6. Effects of Suanzaorentang on sleep (mean±SD)

Variable	No. of Patients	Treatment Period: Placebo	Treatment Period: Suanzaorentang
Sleep latency (min)	52	62±14*	25±10*
Sleep time (hr)	60	4.9±0.7*	7.2±0.6*
No. of intermittent awakenings	38	4.2±1.1*	2.3±0.6*
How well slept#	60	4.2±0.5*	5.9±0.4*
How felt on awakening#	60	4.1±0.3*	5.5±0.5*

1. * Difference between treatments significant ($p < 0.001$; Student's t test).
2. # Based on seven-point scale.
3. During treatment with S-T, all sleep measures were significantly improved; those symptoms accompanying insomnia abated.

Table 7. Effects of Suanzaorentang on MAI, HAS, and DSST

		Before the 1st week		After the 1st week		After the 2nd week
MAI	Mean	27.4		26.2		22.9
	SD	7.1		8.5		9.8
p value			>0.4		<0.001	
HAS	Mean	23.7		21.9		14.2
	SD	6.9		7.3		8.2
p value			>0.1		<0.001	
DSST	Mean	39		42		50
	SD	12		11		10
p value			>0.1		<0.01	

1. All these measures were statistically significantly improved by 2 weeks on S.T.
2. This means that anxiety was decreased and psychomotor performance was improved by S.T.

Table 3 Effects of suanzaorentang, diazepam and placebo on MAI, HAS and 4 HAS subsets scores (Mean ± SD).

Visit	1	2	3	4
MAI				
suanzaorentang	26.4 ± 7.6	25.9 ± 6.7	21.5 ± 8.9*	23.7 ± 8.5
diazepam	28.9 ± 8.2	27.7 ± 7.3	22.7 ± 8.6**	24.8 ± 8.9
placebo	27.4 ± 8.1	27.1 ± 7.5	26.8 ± 8.2	26.7 ± 8.1
HAS				
suanzaorentang	24.2 ± 5.9	23.3 ± 7.2	15.9 ± 8.2***	19.8 ± 6.7*
diazepam	23.6 ± 6.2	22.1 ± 8.1	15.5 ± 7.4***	19.6 ± 8.2*
placebo	24.5 ± 6.0	23.7 ± 7.5	23.5 ± 7.4	23.4 ± 7.3
Anxious mood				
suanzaorentang	2.1 ± 0.4	2.0 ± 0.3	1.0 ± 0.3***	1.5 ± 0.4***
diazepam	2.0 ± 0.3	1.9 ± 0.4	1.1 ± 0.4***	1.3 ± 0.3***
placebo	2.2 ± 0.5	2.1 ± 0.5	2.0 ± 0.5	2.0 ± 0.4
Cardiovascular symptoms				
suanzaorentang	2.4 ± 0.3	2.4 ± 0.4	1.0 ± 0.3***	1.7 ± 0.3***
diazepam	2.3 ± 0.4	2.3 ± 0.3	1.2 ± 0.4***	1.6 ± 0.2***
placebo	2.5 ± 0.3	2.5 ± 0.3	2.4 ± 0.3	2.3 ± 0.4
General somatic (muscular)				
suanzaorentang	2.0 ± 0.3	2.0 ± 0.4	1.6 ± 0.4***	1.9 ± 0.3***
diazepam	1.9 ± 0.3	1.8 ± 0.3	1.0 ± 0.3***	1.4 ± 0.4***
placebo	2.1 ± 0.3	2.0 ± 0.4	2.0 ± 0.3	1.9 ± 0.2
Insomnia				
suanzaorentang	1.7 ± 0.3	1.6 ± 0.2	1.0 ± 0.4***	1.3 ± 0.3**+
diazepam	1.6 ± 0.3	1.5 ± 0.4	0.5 ± 0.2***+	1.0 ± 0.4***
placebo	1.6 ± 0.4	1.5 ± 0.2	1.4 ± 0.3	1.4 ± 0.3

* $p < 0.05$ (visit 3 to visit 2; visit 4 to visit 3), ** $p < 0.01$ (visit 3 to visit 2), *** $p < 0.001$ (visit 3 to visit 2; visit 4 to visit 3), + $p < 0.001$ (diazepam to suanzaorentang)

MAI and HAS score were significantly improved by diazepam and S-T, but not by placebo.

CONCLUSION

(1) The mechanism of Suanzaorentang may be related to its effects on the catecholaminergic and serotonergic systems.

(2) It has no significant effect on the GABAergic system.

(3) The main locus of action might be in the limbic system.

(4) The mechanisms of action of Suanzaorentang are not quite the same as those of benzodiazepines.

CONCLUSION

(1) The sedative component of the Suanzaorentang may be alcohol-soluble.

(2) It significantly prolonged the period from the onset of convulsion to the time of death induced by pentylenetetrazol or picrotoxin.

(3) It significantly prolonged the sleep duration induced by hexobarbital.

(4) It markedly enhanced the hypomotility induced by α-MT.

(5) It markedly reduced the locomotor stimulation produced by L-DOPA plus benserazide.

(6) It improved the mood(by Hamilton Anxiety Scale and Morbid Anxiety Inventory Scale).

(7) It improved the psychomotor performance during the day-time (by Digital Symbol Substitution Test).

(8) It sedative effects are related to the inhibitory effects on the catecholaminergic activity in the CNS. And it is a promising anti-anxiety drug.

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